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No. 1

Original Articles

A PATHOLOGIC STUDY OF THE LUNGS IN ONE HUNDRED AND FIFTY-TWO AUTOPSY CASES OF SYPHILIS*

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(Received for publication, November 19, 1919.)

PULMONARY syphilis still remains today a doubtful and little explored field for the medical practitioner. Nevertheless, clinical diagnoses of syphilis of the lungs are much more frequently made than they are given a pathologic confirmation at the autopsy table. In view of the apparent increasing interest among clinicians as to the frequency of involvement of the lungs in syphilis, it is of the greatest importance to attack this problem from the standpoint of the new pathologic criteria set up by such investigators as Warthin, Fordyce, and others. This has not yet been done; and the object of this paper is to make an attempt in this direction.

HISTORICAL SURVEY OF PULMONARY SYPHILIS

Morgagni stated that the lungs were frequently injured by the lues venerea. Syphilis of the lungs as a distinct affection, how-

*From the Pathological Laboratory of the University of Michigan.

ever, was first mentioned by *Zadig*, in a paper published in Jena in 1797. Following this, the main publications upon pulmonary syphilis before 1900 were those of *Bayle* (1810-12), *Munk* (1841), *Guirac* (1877), *Negri* (1868), *Huchard* (1873), *Frey* (1876), *De Bonilla* (1876); *Poggio*, *Porter*, *Samid* and *Nogueire* in 1877; *Lancereaux* (1878), *Hanop*, *Sacharjiss*, *Seyler*, *Perry* ("syphilitic fibrosis") before 1890, and *Foulard* in 1893.

The diagnosis of syphilis of the lungs made by these writers, the older ones, as well as the most recent, will not survive any critical examination. Tuberculosis, brown induration of the lungs (once regarded as a syphilitic lesion), chronic lymphangitis (which *Cornil* considered to be syphilitic), gangrene and other conditions were confused with luetic lesions. The diagnosis rested either upon the macroscopic appearances alone, or upon the fact that the pulmonary condition occurred in a person affected with lues. In other cases gross mistakes of diagnosis were made, the conditions described were quite evidently other than syphilis. Among the cases of this class may be mentioned those of *Hedenius*, *Wilks*, *Belin*, *Chvostek*, *Randohr*, and four of the five cases reported by *Tiffany*.

Of other writings upon pulmonary syphilis may be mentioned those of *Lancereaux*, *Landria*, *Parrot*, *Schnitzler* and *Pancritius* before 1900, *Marfan* in 1901, *Hänsemann* and *Kokawa* in 1905. The best collective articles upon the subject are those of *Massia*, *Herxheimer*, *Brandenburg* and *Flockemann*.

An analysis of all the reported cases of pulmonary syphilis reveals the following in so far as frequency, type of lesion, inception and progress of the affection, occurrence of gumma of the lungs, etc., are concerned.

1. *Frequency of Syphilis of the Lungs*.—An examination of the collections and records of pathological laboratories and museums would seem to show that pulmonary syphilis is one of the rarest conditions. According to *Claytor*, in 1905 out of 13,000 specimens at the Army Medical Museum in Washington there was not a single example of pulmonary syphilis. In 1895 in the pathologic collections in London there were but ten cases placed under that label. Neither *Ford* from the Massachusetts General Hospital nor *Otis* in his practice found a single case of pulmonary syphilis. In 6,000 autopsies in Chicago, *Backok* reports but two cases showing

syphilitic lesions of the lungs. *Kolisko* of Vienna saw one hundred cases of lung syphilis in thousands of autopsies. *Dorsey* found none in a series of several hundred. *Symmers* found two cases of "chronic catarrhal pneumonia" due to syphilis in a series of 314 autopsies on syphilitic cases. In 4270 autopsies at the Pathologic Institute in Buenos Aires syphilis of the lungs occurred extremely rarely. In 1911, *Stanley* found two cases of syphilitic pulmonary lesions and one doubtful one among 1,000 cases of pulmonary disease. *Chiari* observed one case of syphilitic lesion of the lung in 98 autopsies on syphilitic subjects. *Osler* saw twelve cases in 280 autopsies on syphilitics at the Johns Hopkins Hospital. *Peterson*, in 1893, found eleven instances of pulmonary syphilis out of 88 cases.

It is evident that the incidence of pulmonary syphilis depends upon the personal criteria of the investigator, the year in which the investigations were made, etc. The multiform variety of the lesions of syphilis increase the difficulty of diagnosis; and these various factors explain the wide differences of investigations, as shown by 61 cases (only one of which was gumma) out of 2,995 of *Stolper*, and the 1 out of 1000 cases of *Hunter*, *Ehlers* and *Wires* giving the lungs the last place as the seat of syphilitic lesions; in striking contrast to this view is the belief of a modern writer, *Rössle*, that syphilis of the lungs is at least as frequent as syphilis of the liver.

If we were to accept the statements of the clinical men, there would be found to be an astonishingly large number of cases diagnosed as syphilis of the lung and the tendency to make clinical diagnoses of pulmonary syphilis seems to be increasing. Undoubtedly many of these cases were given such a diagnosis upon insufficient grounds, and some writers have exaggerated the clinical frequency of pulmonary involvement in syphilis. In four years service under Doctor *Azua* of Madrid, I did not see a single case of pulmonary involvement that could be ascribed to syphilis out of some hundreds of syphilitics. I am inclined to agree with *Dieulafoy* that the clinical diagnosis of syphilis is largely dependent upon the power of intuition possessed by the practitioner. *Stengel* also has stated, to the same effect, that the discrepancies as to the incidence of pulmonary syphilis are dependent upon conditions appertaining to the investigator; the pathologist finds

it more rarely than the clinician; the diagnosis of syphilis is more easy and certain at the autopsy. Nevertheless, as *Flockemann* says, there is no good reason why the lungs should not be attacked by lues as frequently as any other part of the body. In more recent cases x-ray examinations have given more assurance to the diagnosis. As far as incidence according to sex is concerned, all writers, as is logical, agree that pulmonary syphilis is more frequent in men than in women, just as they all say that clinical syphilis is more frequently found in the male sex.

2. *Types of Pulmonary Syphilis According to the Authors.*—Two types of lesion, the gumma and fibrosis, are the chief conditions described by the authors, but very different conceptions of these conditions exist among them. Some authors, as *Cornil*, denied the occurrence of pulmonary gumma; others, as *Lagneau*, describe not less than seven different kinds of syphilis of the lung. *Dieulafoy* regarded as syphilitic a bronchopneumonia, cavitary form, fibrosis with bronchial dilatation, and two related forms, gangrene and syphilitic pneumopathy, coincident with pulmonary tuberculosis. To the two main types of lesion, the gumma and fibrosis, accepted by *Mauriac*, *Orth* added an ulcerative and indurative (sclerotic) form. *Neumann* added a "diffuse form;" *Fraenkel* a "catarrhal form;" *Osler*, *Lancereaux* and *Aufrecht* accept the two main types, but the last-named regards the fibrosis as a pneumonia and subdivides it into "interstitial" and "parenchymatous" forms.

More recently new conceptions have arisen, as shown by the terminology applied to the designation of the syphilitic lesions. For example, *Reilly* says that tracheo-bronchitis and profound syphilis are the main forms of pulmonary syphilis; the lesions would consist of gumma or localized or diffuse exudative lesions, leading to fibrosis. Arteritis would always accompany these processes. As to the so-called "syphilitic phthisis," recent authors as *Morris* and *Rössle* accept it, the latter giving as a frequent finding a type of pneumonia resembling the syphilitic "white pneumonia" of the newborn.

All of these classifications with varying terminology are, save rare exceptions, but mere words, and we must agree with *Warthin* that our knowledge of lung syphilis is very incomplete. We are still as in the time of *Pancritius*, or but little more advanced. Said

Pancritius, "Syphilis of the lung consists in a swelling, thickening, hypertrophy, hyperplasia of the interstitial, interalveolar, peribronchial tissues of the lung."

3. *Spirochetes in Lung Tissue*.—The spirochete pallida has been found in the lung of congenital syphilitics by many workers, and is a matter of routine pathologic demonstration; but, as far as I know, the only positive findings of spirochetes in the lung-tissue of acquired syphilitics are those of *Koch*, *Schmorl* and *Warthin*. The finding by *Buchanan* of spirochetes in the sputum of a case of pulmonary syphilis is questionable.

4. *Inception of Pulmonary Syphilis*.—*Dann* of Amsterdam first described pulmonary syphilis precox; and many papers have since been written upon this from the clinical side (*Schnitzler*, *Schirren*, *Rothschild*, *Gwyn*, *Chantemesse*, etc.). While these writers have discussed the early symptoms and x-ray findings of pulmonary conditions in the second stage of syphilis, no autopsy studies have been discoverable. *Stanley* says that in the first stages of lung syphilis there is a diffuse mediastinitis, with intense cell proliferation filling the alveoli, and infiltrating the septa, peribronchial and perivascular tissues, with epithelial desquamation, giving a gelatinous appearance to the portion of lung involved; in other words, the lesion is a syphilitic acute interstitial pneumonia. In general the opinion of writers upon this subject is represented by *Rössle* who says that the early stages of the lesion are unknown.

5. *Gumma of the Lung*.—The reported case of pulmonary gumma in the literature show an evolution from purely gross diagnostic points to more detailed microscopic descriptions. *Ranvier*, *Budd*, *Dumoulin*, *Wilks*, *Spencer*, *Wells*, *Hutchinson*, *Jackson*, *Lebert*, *Howitz*, *Hecker*, *Hertz*, *Karnbach*, and *Nachs* recorded observations on lung syphilis with descriptions of the gross pathologic anatomy of the gumma. *Cornil*, *Ranvier*, *Wagner*, and *Pidoux* attempted to differentiate macroscopically between syphilis and tuberculosis of the lungs. But undoubtedly many of the diagnoses of gumma based upon macroscopic criteria were incorrect; as for example *Hiller's* finding of 9 cases of gumma of the lungs in 87 cases of syphilis.

Lancereaux regarded the multiplicity, size, grayish color, irregular form, firm consistency (slightly elastic), and the inclusion of the gumma in an indurated area poor in vessels, as diagnostic criteria. He accepted also the possibility of expulsion of a gumma

per vomica. In *Maunoir's* case the diagnosis was made by *Malassez* on the ground of collections of small cells as in gummas of the other organs. *Dieulafoy* refers to a case in which many nodules were scattered through a very hard tissue. *Schutz* describes a case with caseation; and *Henop* cases of peribronchial and subpleural caseations, with increase of connective tissue and narrowing of the bronchi. In *Randohr's* case syphilitic pneumonic infiltration and caseation were present; he calls attention to the endarteritis, the vascularization and pleural infiltration. *Pavlinoff* described the infiltration as made up of spindle and round cells without giant cells, the perivascular process being the chief feature. *Nicholson* found calcification but no caseation. In *Salomon's* case the elastic tissue of the lung supported the sclerogummatous tissues. According to *Shingu*, *Störch*, and *Robinson* the arterial lesions form the chief features for the diagnosis. While almost all of the writers mentioned, as well as *Herxheimer* and *Balzer*, found a fibrosis, *Shingu* observed some of the lesions in his case without this reaction. *Hänsemann* accepts the occurrence of regressive changes, while *Hecker* denies them.

Of the more recent writers, *Osler* describes the gummatous lesions as showing minute patches of caseous necrosis in the neighborhood of a vessel showing arteritis. Later there is a capsule formed, and at the same time the pneumonic process develops. Microscopic examination shows the absence of fibrous connective tissue at the periphery, with an infiltration of round cells and an active proliferation. Within the alveoli a cubical epithelium is formed without any giant cells. When giant cells are present they are different from those found in tuberculosis. *Tanaka* and *Patino* give the most modern description of the pulmonary gumma, emphasizing the presence of the plasma cell in the active lesions. All of the recent writers admit the possibility of caseation of the gumma, and some of them, as *Marshall*, accept the possibility of its evacuation through the bronchi. *Clayton* states that the macroscopic appearances of the gumma vary with the stage of its development; it may be a gelatinous mass or nodule of a grayish white color, or yellow, or red, surrounded by a more or less well-defined capsule formed after inflammatory changes.

The great majority of the description of pulmonary gummas were concerned only with the gross appearance. The microscopic de-

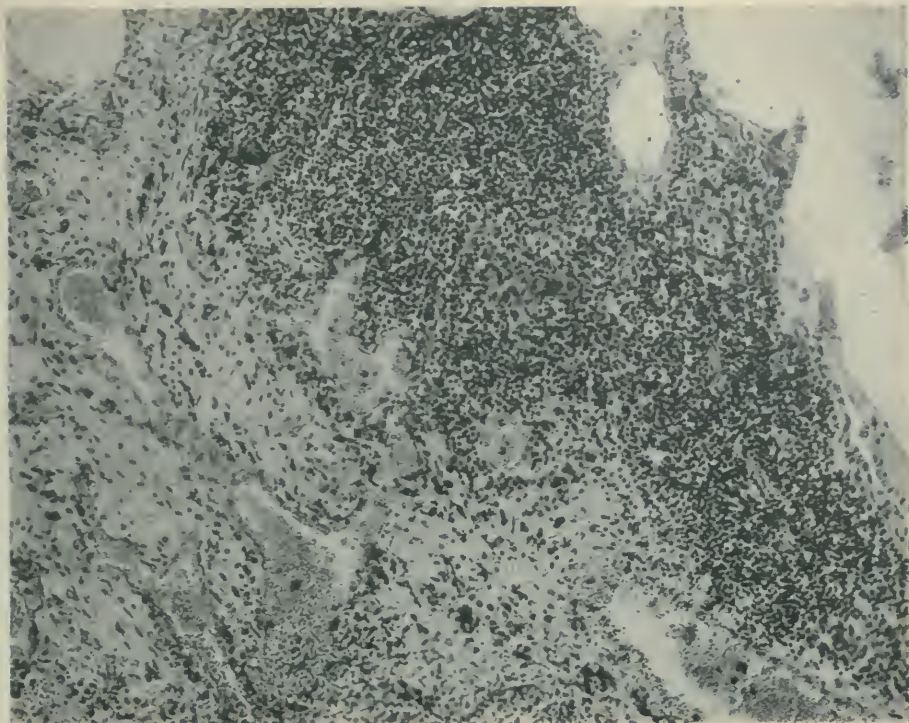


Fig. 1.—Active miliary gumma in lung showing marked syphilitic fibrosis.

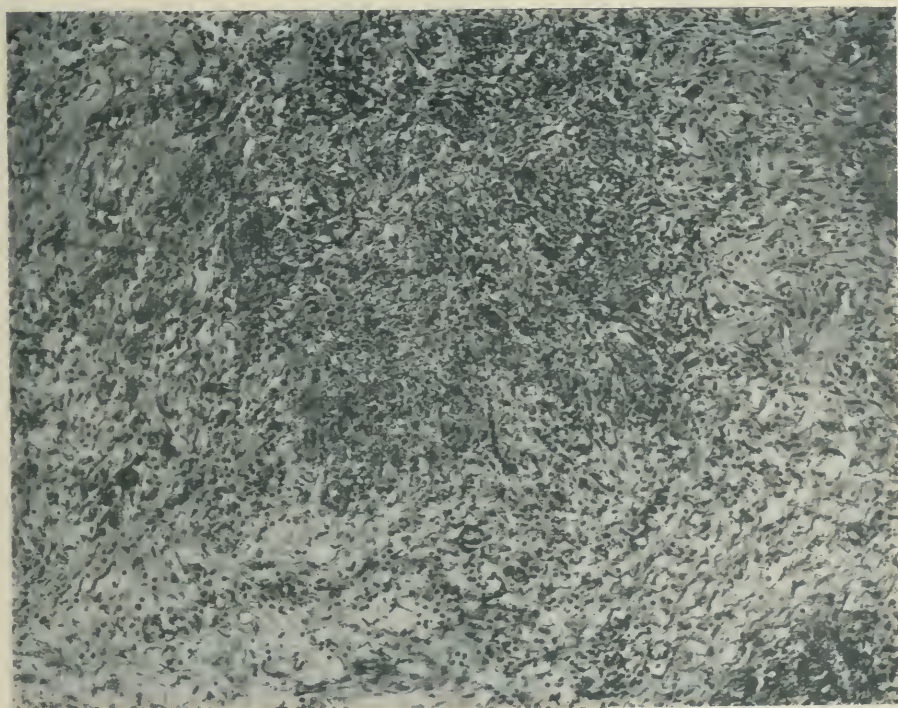


Fig. 2.—Fully developed noncaseating gumma of lung, showing the central vascular area that is just beginning to degenerate.

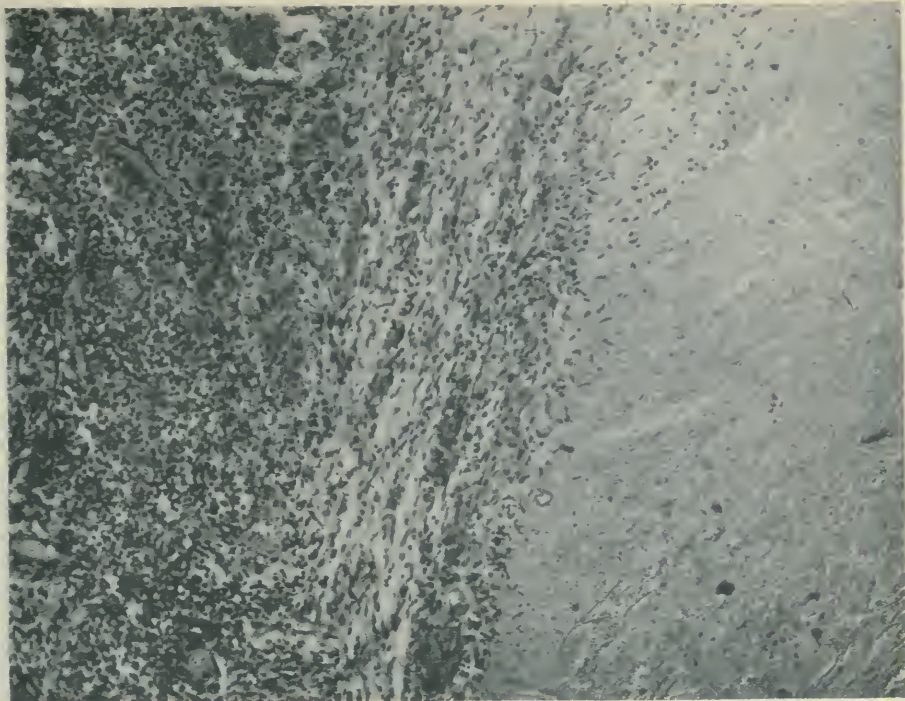


Fig. 3.—Fully developed caseating gumma of lung, showing the three zones.

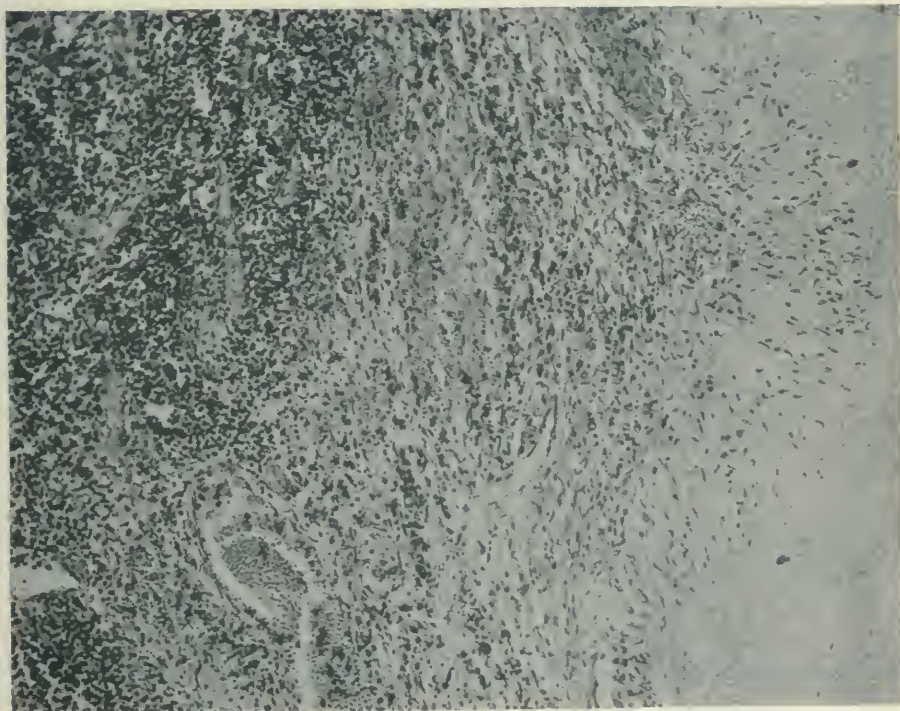


Fig. 4.—Fully developed caseating gumma of lung showing the three zones, the peripheral plasma cell zone being particularly well marked.

scriptions, as a rule, mention the three zones of central degeneration, a caseation, an intermediate one of neoformation, and an outer one of transition or infiltration. It is a very striking fact that in the majority of cases described microscopically the gumma is found in combination with an interstitial fibrosis or sclerosis; there is an accompanying arteritis, a peripheral infiltration of round cells and plasma cells, with a preservation of the yellow elastic fibers in the central zone of caseation. Giant cells are usually few. Of the macroscopic descriptions many are not sufficiently defined to permit any distinction being made between the tubercle and gumma. Some of the points emphasized by the authors as characteristic are the multiple occurrence of the gumma, its subpleural or peribronchial situation, the congestion zone about it, the concomitant pleural thickening, and the extraordinary cicatrization of the lesion.

6. *Location of the Gumma.*—Hyde says that a gumma never appears at the apices of the lungs. Tanaka, however, admits such a possibility, although the great majority do not appear there. Kaposi, Brandenburg and Rolleston state that the gummatous lesions are chiefly peribronchial and subpleural; Fowler, on the contrary, describes them as in the substance of the lung. All of the writers agree that the right lung is more frequently affected (Grandidier, Hirsch, Sacharjiss, Pancritius, Pavlinoff, Cube, Salterthwaite, Carlier, etc.). Rössle states that the upper or lower lobes are usually involved, while others (Grandidier, Cube, Aufrecht) have found the middle lobe also involved.

7. *Gumma in Congenital Syphilis of the Lung.*—Many writers have described gummatous lesions in the lungs of congenital syphilites (Apert, Zuber, Martineau, Depaul, Wagner, Lancereaux, etc.). There may be a combination with white pneumonia, peribronchial sclerosis, or even with tuberculosis. Cases showing all three of these combinations occur in the material of the Pathological Laboratory of the University of Michigan.

8. *Diffuse Syphilitic Pneumonia.*—The literature shows a great deal of discussion over the so-called lobular syphilitic pneumonia of the adult. Some of the cases were examples of syphilitic infection extending from the liver lesions (Bruhl, Galvagni, Delépine). The lesions of the lungs, as described, resembled those of congenital syphilitic pneumonia. Virchow was unable to differentiate such a syphilitic pneumonia, and the majority of writers have followed

his dictum. *Gambrini*, *Gwyn*, and others regard it as a simple pneumonia. On the other hand, *Neumann* accepted the existence of a specific pneumonia, and described it as having an acute catarrhal or croupous form, atypical in development and yielding to the treatment of syphilis. *Robinson* also accepts this type of pneumonia, and *Fowler* describes it as a caseous area including many round cells.

Councilman thinks the syphilitic process opens the way for some other infection. *Tanaka* denies the existence of a specific syphilitic pneumonia. *Sokolowsky* says that in many cases a pneumonia due to a different cause is added to the pulmonary process. *Birch-Hirschfeld*, *Rollet*, *Orth*, *Davidson* and *Kaufmann* likewise assert that there is not a primary syphilitic pneumonia. *Adami* admits the possibility of a combined pneumonia and pulmonary syphilis.

Among the descriptions given by various authors of combined syphilis and pneumonia is that of *Councilman*, who describes hyaline changes in the capillary vessels, distended alveoli, atrophic alveolar walls and fibrin formation, obliteration of the capillary lumina, new-formed connective tissue around the bronchi and arteries, caseous degeneration, and ultimately fibrosis and sclerosis. Gummas may be present. *Patino* accepts this type of pneumonia, but regards it as a chronic process; when acute he considers it to be due to some other cause. *Witherspoon* describes a form with connective tissue changes, intense cellular proliferation filling the alveoli, with infiltration of the alveolar septa, peribronchial and perivascular tissues. The macroscopic appearances of this form of syphilitic pneumonia are described by *Massia*, as follows: the lung has a gelatinous aspect with one of the lobes hard, heavy, airless, gray or grayish red in color. *Killer*, who was the first to describe this gelatinous appearance, admitted that it could be produced by an interstitial infiltration of the alveolar walls, or by a desquamative catarrhal process; the first he regarded as syphilitic, the second form as due to an added infection. There can be little doubt, I think, that some of these cases, as well as those of *Dieulafoy*, *Raymond* and *Kirchheim* are in no wise different from ordinary pneumonias. Likewise, the descriptions given by *Robertson* and *Aufrecht* of especial types of cells, pigmented giant cells, etc., apply to many early forms of pneumonia, and are not typical of syphilis.

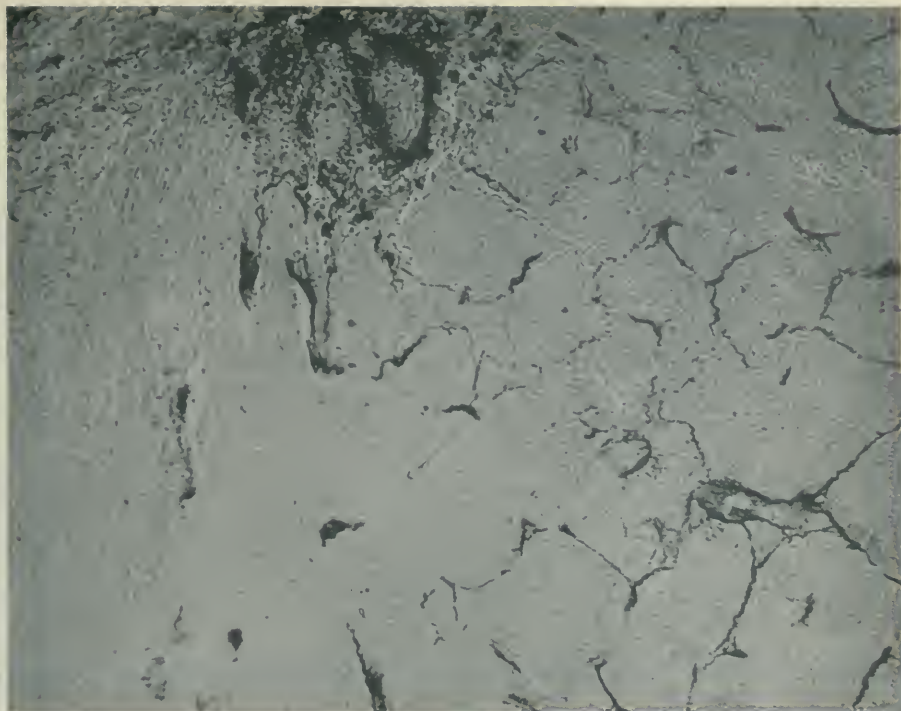


Fig. 5.—Yellow elastic tissue stain of central caseating zone of gumma, showing preservation of the elastic tissue of the old alveolar walls and new formation in blood vessel wall.

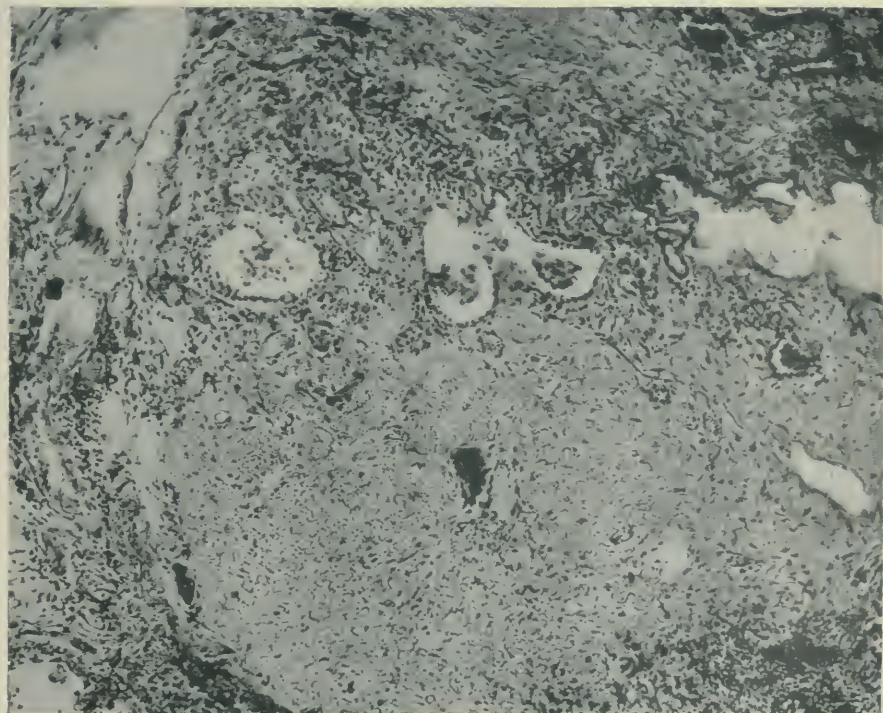


Fig. 6.—Scar of gumma. In the periphery of the scar are alveoli showing the hypertrophic cuboidal epithelium.

9. *Syphilitic Caseous Pneumonia*.—Some authors go much farther, and assert the existence of a typical syphilitic caseous pneumonia. (*Fournier*). (*Councilman* saw a case of this kind in which caseous pneumonia with desquamated epithelium and necrotic cells was associated with hyaline degeneration of the alveoli and endarteritis. At the present time the majority of writers deny the existence of a syphilitic lesion of this type (*Hochsinger*, *Salomon*, *Beriel*, *Orth*, *Tiffany* and *Hertz*).

10. *Lymphangitis Syphilitica*.—Many writers have regarded lymphangitis of the lung as syphilitic in type, as seen by *Weber*. *Hänsemann*, however, demonstrated the occurrence of this lesion in non-syphilitic cases. It may be in some cases a syphilitic lesion. *Rössle* recently has called attention to the possibility of confusion of this type of lesion with the so-called syphilitic pneumonia.

11. *Muscle Cirrhosis*.—*Brown Induration*.—*New formation of Muscle*.—*Virchow* called attention to the fact that brown induration of the lungs occurs in syphilitics, and he thought the condition might be due to syphilis. The so-called “*muskuläre cirrhose*” or “*carnification*” of the lung of the German writers falls in this class. In these conditions the alveolar walls are thickened, and some writers believe that there is a new formation of smooth muscle. *Kaufmann* saw cases which he attributed to syphilis; *Brühl* demonstrated that it occurs in nonsyphilitic cases; and *Davidson* thinks that the *muskuläre cirrhosis* is the result of pulmonary congestion and not due to syphilis. *Tanaka* emphasizes the new formation of smooth muscle fibers near the middle divisions of the bronchi, surrounding the bronchi and the alveoli, and extending into their lumina, and tending to the hardening of the lung tissue, eventually pulmonary sclerosis. *Rössle* says that in one type of syphilitic pneumonia this new formation of smooth muscle is typical (*muscular cirrhosis*), extending into the alveolar walls and subpleural tissues. *Stöhr* finds smooth muscle fibers normally throughout the lung trabeculæ, but not in the alveolar walls (although present here in the reptilian lung), so that the appearance of this muscle in pathologic conditions is due to a hypertrophy of preexisting fibers, and not to a new formation. *Massia*, *Patino*, and the majority of writers apparently believe in a new formation of muscle in the peribronchial, interalveolar and perivascular tissues, arising either from the bronchial muscle or from that of the hyper-

trophic blood vessel walls. In the latter case it may have no connection with syphilis.

12. *Chronic Interstitial Pneumonia.—Sclerosis.*—As *Patino* has very well stated, syphilis is a disease of chronic evolution and inflammatory reaction, with a tendency to the new formation of connective tissue, particularly in relation to its effects upon the lungs. *Delafield*, in his text-book says that syphilis can be marked in the lung as a diffuse formation of fibrous connective tissue. Even in the time of *Lancereaux* syphilitic scars of the lung were accepted. *Laënnec* in his "Traité de la Auscultation" gave a number of such cases. *Andral*, *Lancereaux*, *Greenfield*, *Gowers* (this case, in my opinion is one of tuberculosis, as shown by the drawings), and *Green* presented cases of this kind. In *Green's* case the fibroid formation began around the blood vessels, the vascularity of the tissues distinguishing it from tuberculosis. *Pye-Smith* described a case in which contraction of the bronchi was present; and *Mahomed* published two cases with small cell growth and fibrosis; and concluded that many undiagnosed cases might present the same picture. *Osler* thought that fibrous syphilitic bronchitis might be an extension from the pleura. *Weber* reported two cases in which both lungs were fibrosed. *Stanley*, in one of his cases described such a fibrosis without concomitant large gummas as in his other case. Such forms of pulmonary sclerosis have received many names; *Neumann* called it chronic interstitial pneumonia; *Mauriac*, sclerosis of the lung; *Orth*, indurative pneumonia; *Cartier*, hyperplastic sclerosis; *Fraenkel*, diffuse induration. *Virchow* denied that such fibrosis could be ascribed to syphilis. *Ziegler* thought that a part of such conditions might be due to syphilis, the remainder to other causes. This is the prevailing view.

Henske Sforza said that this pneumonia could have a lobar form, but such observation has not yet been recorded. *Massia* described the lung of interstitial pneumonia as showing a fine network of sclerotic tissue, creaking under the knife, and most prominent in the middle lobe in the interlobular trabeculæ. *Hänsemann* describes as typical the ray-like arrangement of the fibers. *Councilman* agreed with *Neumann* as to the form of the "poumon lobulé" of the latter author. *Lord* states positively that the picture of these forms of pulmonary fibrosis is not typical of syphilis. The characteristic conditions that have been described as typical are, as follows:

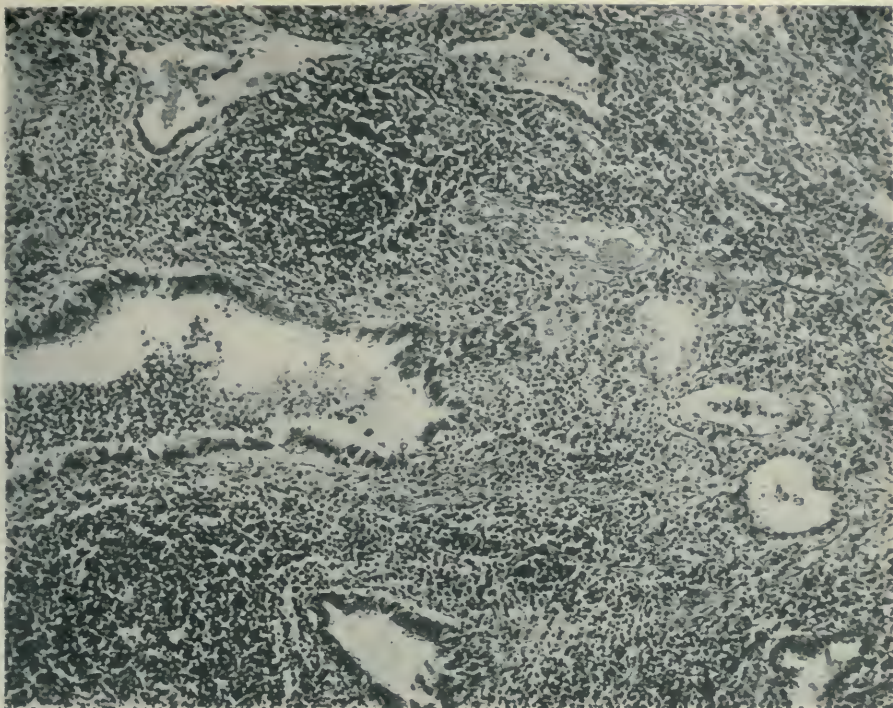


Fig. 7.—Active syphilitic peribronchitis and interstitial pneumonia. Marked hyperplasia of the primitive lymph nodes, diffuse plasma cell infiltration and fibroblastic proliferation. Spaces lined with cuboidal epithelium.

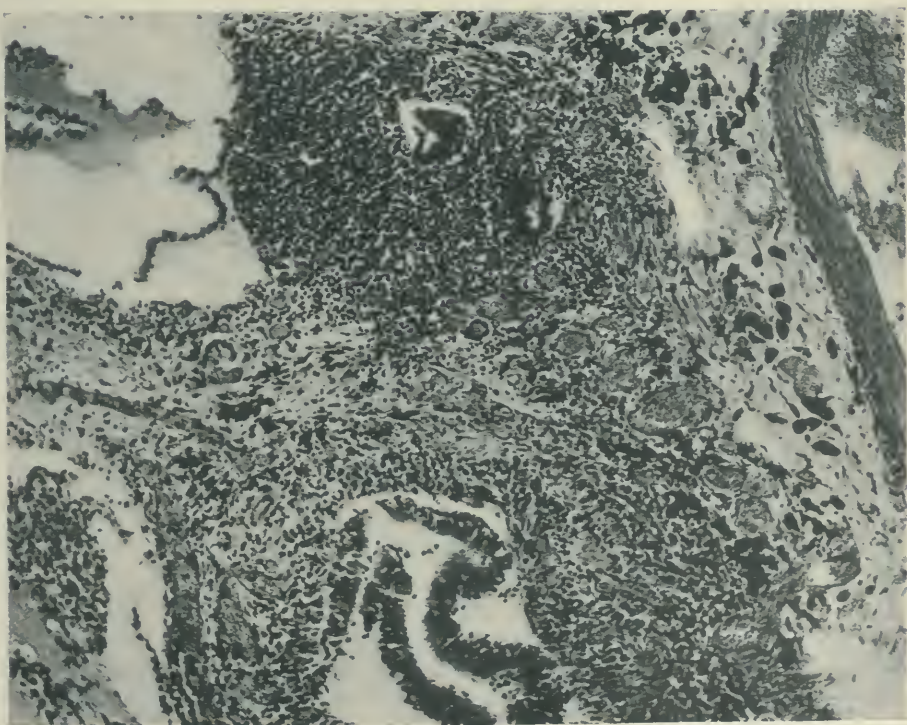


Fig. 8.—Syphilitic infiltrations and proliferations in bronchial wall.

a diffuse infiltration localized in the middle portion of the lung, red-yellow in color, of varying shades, smooth, uniform, airless, compact, or nodular with sclerosis of the bronchi, which may be dilated; the sclerotic tissue radiates from the hilum or from the pleura, and can extend to the farthest zones of the lungs; it can form septa of the 3rd and 4th order, giving to the lung a lobulated aspect; the sclerosis is produced by a connective tissue which compresses the alveoli. Round and plasma cells, endarteritis, and perhaps pigmented phagocytes complete the picture; around the bronchi and vessels the thickening is constantly found; and in some places the alveolar walls are thickened. The elastic tissue is very well preserved, and new muscle fibers can be formed along the vessels and in the middle part of the bronchi. All writers agree that the bundles of connective tissue radiate from the pleura, in many cases crossing the lung from side to side.

Pye-Smith regards peribronchial gummas or plaques as the starting-point of the process, and the bronchiectasis as a result. In *Mahomed's* case the remains of a syphilitic infiltration could be seen; giant cells were present. Also in *Rolleston's* case it was easy to demonstrate that the gumma was the first step in the process and *Flockemann* says that this is always the case. The scar tissue can be in isolated patches, or generalized in extensive areas, or diffuse. In many cases, as in *Störck's* the pulmonary cirrhosis alone is evident; in other cases, as in *Petersen's* gummas are present also.

Rössle has lately asserted that the characteristic changes in chronic interstitial pneumonia are peribronchitis and periangitis, thickening of the alveolar walls, increase of pigmentation, and new formation of a network of connective tissue. The lesion affects chiefly the lower lobes; beneath the epithelium there is a new formation of connective tissue; bronchitis with bronchiectasis is present; no secondary collapse of the lung takes place. He affirms that the early stages of the lesion are imperfectly known (in my opinion the picture he gives of such early stages is more like that of early tubercle than of gummatous infiltration). *Rössle* admits the possibility of a macroscopical recognition of the process, because the bronchi appear as white points; the bronchial nodes have a cornified aspect typical of syphilis, with hyaline thickening. The pleura may be smooth, or thickened, the infiltra-

tion is most marked about the bronchi, vessels and interlobular septa. In its early stages this interstitial process is recognized with great difficulty. Some writers believe that the earliest stage is a perilymphangitis, as in *Hamann's* case, in which the lymphatic cords were thickened with perivascular new formation of connective tissue which later would result in sclerosis. It is known that the sclerosis is often preceded by gummatous infiltration and subsequent cicatrization. *Stanley* says there are two kinds of pulmonary sclerosis, one in which the increase of connective tissue takes place in the alveolar walls, with miliary gummas, and elastic proliferation forming a thick net-work about the bronchi and pleural vessels; in the second form the lung is contracted, misshapen, without visible gummas.

I must remark here that the writers mentioned above do not differentiate these lesions from those of tuberculosis or anthracosis on a basis corresponding to our actual knowledge of syphilis. Finally, we may consider the "gray induration" of *Massia*, in which were pigmented macrophages (*Mosny*), epithelioid and giant cells of the type regarded by *Nicolas* and *Favre* as not tuberculous in type. Other writers have noted the finding of pigmented phagocytes, but that is possible in different pulmonary processes.

13. *Syphilitic Phthisis*.—There has been much discussion over the existence of a so-called syphilitic phthisis; the earlier authors considered this the only type of syphilitic lesion of the lungs. *Hoffmann* was the first observer; with his findings agreed *Lagneau*, *Ricord*, *Graves* and *McCarthy*. *Astruc*, *Sauvage* and *Morgagni* advanced the possibility that the lesions of syphilis would prepare the way for tuberculosis, and in this way they explained many of the cases. Many authors, as *Sokolowsky*, agree that many of the supposed cases of syphilitic phthisis are in reality tuberculosis. Other writers (*Rollet*, *Stoicescu*, *Hänsemann* and *Cube*) admit the possibility of a sclerotic syphilitic tissue with cavern formation, and have described cases of this kind. The pathology of syphilitic phthisis would consist of peribronchial fibrosis, emphysema, fibroid bands, bronchial dilatation, and formation of cavities opening into the bronchi. *Hiller* described a case showing such findings. *Osler* and *Gibson* state that bronchiectatic cavities may be associated with a syphilitic pneumonic process, and that a lung may be ex-

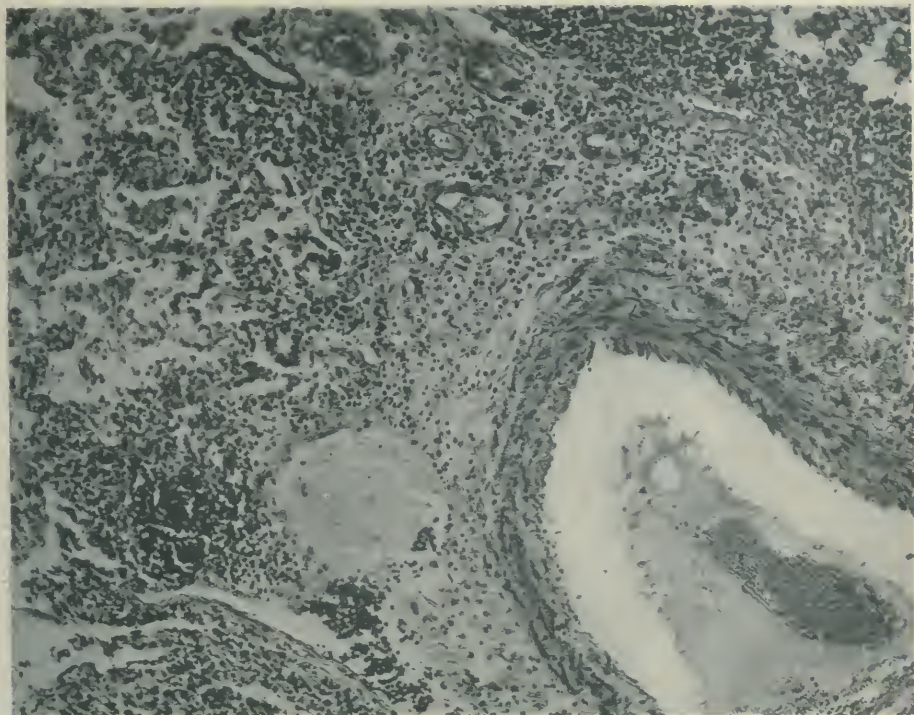


Fig. 9.—Perivascular syphilitic fibrosis and infiltrations in lung. Spaces lined with cuboidal epithelium.

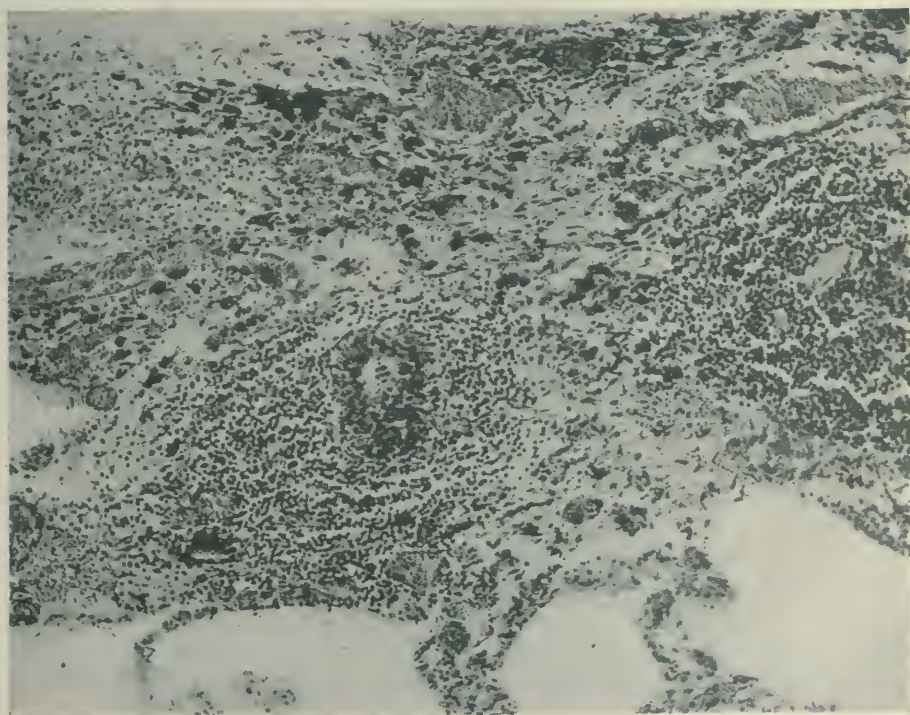


Fig. 10.—Nearly completely obliterated bronchiole due to syphilitic plasma cell infiltrations and fibrosis. Heavy anthracosis in the neighboring connective tissue.

cavated by a bronchial dilatation in the same way as occurs from an aneurysm.

Gangrene of the lung has also been attributed to syphilis. *Caster* has published cases; the endarteritis may be taken as a cause of the gangrene.

14. *Bronchial Lesions*.—The occurrence of syphilitic lesions (thickening) of the bronchi has been emphasized by many writers (*Lancereaux*, *Ewart*, *MacKenzie*, *Kopp*, *Fraenkel*, *Wright*, *Duplout*, *Petersen*, etc.). *Councilman* saw a subepithelial connective tissue increase in the small bronchi with an infiltration of lymphocytes and plasma cells, the new formation projecting into the lumen as polypoid formations rich in blood vessels. Many writers have ascribed a syphilitic origin to bronchiectasis (*Bullrich*, *Grawitz*, *Bronchut*). *Corner* found nine cases of bronchiectasis in 56 cases of syphilis. He attributes the condition to the retraction of the lung tissue resulting from the sclerosis. *Rössle* affirms that syphilitic bronchiectasis is the most frequent form known; associated with the bronchiectasis there would be found the remains of the syphilitic infiltration without giant cells. The anthracotic condition of the lung he considers of great importance. *Patino* found plasma cells in the connective tissue of one case, also the cuboidal cells emphasized by *Tripier*, with endarteritis and periarteritis. Similar infiltrations were found by *Delépine* in one case. In *Beriel's* cases there is an easy confusion with tuberculosis; this he recognized himself. Undoubtedly some of the cases reported are those of congenital syphilis of the lung, although appearing in adults. From tuberculosis the diagnosis is made possible when milary gummas are present with a syphilitic infiltration (*Rössle*).

15. *Cuboidal Alveolar Epithelium in Syphilis*.—The alveolar epithelium in pulmonary fibrosis or sclerosis often appears cuboidal, or even low columnar, gland-like. This has been noted by many observers (*Beriel*, *Dutsch*, *Tripier*, *Favre*, *Gawietz*, etc.). *Tripier* thought they were characteristic of syphilis. *Favre* saw them lining cavities in two cases of pulmonary syphilis; he did not consider them as representing any regeneration of the alveolar epithelium. *Gawietz* saw them in the lung of congenital syphilis. *Massia* found these alveolar new formations in sclerotic tissue of the syphilitic bronchiectasis. Such epithelial new formation may be massive in character, even so large as to form new lung tissue in cases of white

pneumonia (*Robin, Lorain, Malassez and Vierling*). *Rössle* regarded them as regenerating epithelial forms in cavities. *Tanaka* noted that in some of his cases some alveoli would be compressed by the sclerotic tissue and would disappear; in others the lumen only would be compressed, and would remain as a mere fissure or star-like opening, in which the epithelium would become cuboidal. *Stroebe, Schultz and Spanudis* think that these cells are fetal rests; other writers, as *Hochsinger*, regard them as cells separated by the sclerosis. These cells are found in many different processes (*Kockbart, Beriel, Eppinger, Rössle*). They are common in all chronic fibroid pneumonias, chronic fibroid tuberculosis, etc.; they represent regeneration or hypertrophic alveolar epithelium, and have nothing specifically to do with syphilis.

16. *Syphilitic Lesions in Pulmonary Arteries*.—*Warthin* has given a recent complete review of the reported cases of syphilitic lesions in the pulmonary arteries, reporting a case of his own with aneurysm of the artery and demonstration of spirochetes in the wall of the aneurysm. Gumma of the pulmonary artery has been reported by *Weber, Wagner, Sequiera and Hanford*; gummatous arteritis by *Schwalbe, Kasem-Beck, Wagner and Quiatkowski*, and *Winternitz and Schmeisser*; nongummatous arteritis by *Thorel, Henschen, Rogers, Dickinson, Payne, Wallace, Friedrich, Grigorjew, Loveland, Brüning, Wagner and Quiatkowski, McPhedran and MacKenzie, Ribbert, Westenhoeffer, and Brooks*. Cases of aneurysm of the pulmonary artery with suspected syphilitic etiology occur in the literature, but *Warthin's* case is the first one in which this etiology has been positively demonstrated. *Birch-Hirschfeld, Greenfield and Petersen* have described the vascular changes in pulmonary syphilis as a meso- and endarteritis. *Pavlinoff* found vessels with obliterated lumina. *Lindwahl* gave a great importance to the endarteritis of the small arteries. *Sugai* states that in syphilitic arteries of the pulmonary vessels the middle coat is chiefly affected, together with the adventitia. *Kokawa* emphasizes the point of origin of every gumma around the vessels; he could see no difference between the arterial changes in tuberculosis and those in syphilis. *Warthin's* study has shown that syphilis of the pulmonary artery is essentially a mesarteritis and periarteritis, with histologic features identical with those of syphilitic mesaortitis.

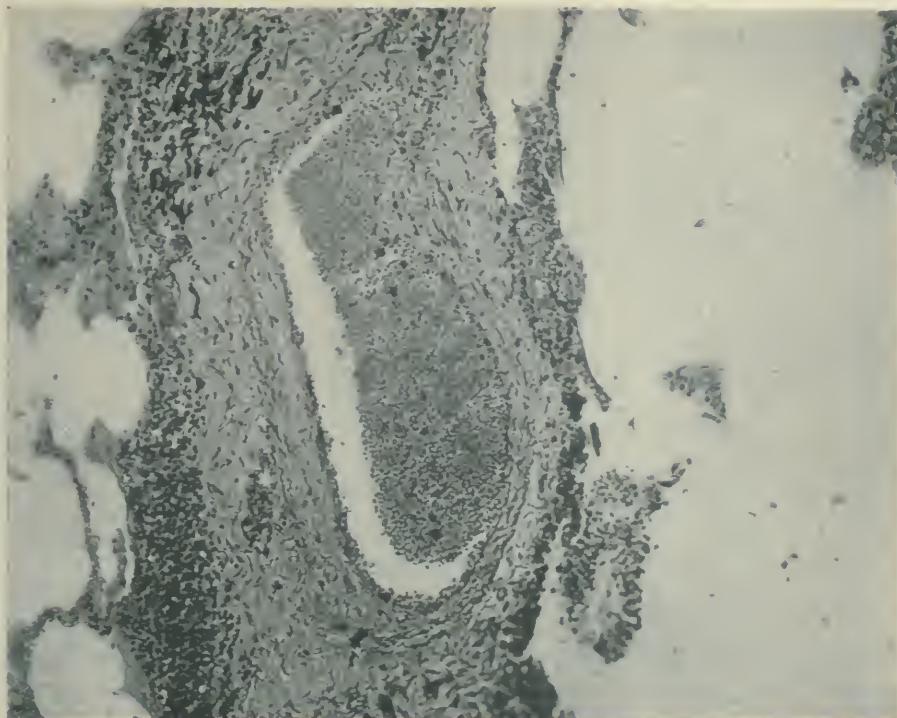


Fig. 11.—Syphilitic lesions in small pulmonary artery.

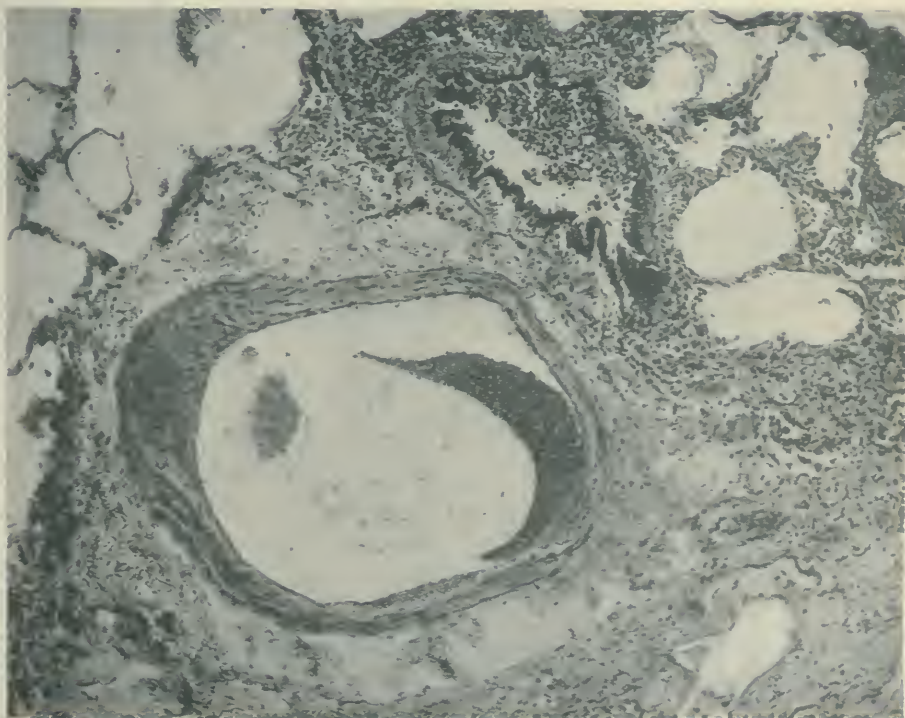


Fig. 12.—Changes in small artery and neighboring tissue in syphilis of the lung.

17. *Lesions of the Pleura.*—The older authors believed in the existence of a specific syphilitic pleuritis (*Lancereaux*). (*Orth, Hänsemann* and *Rolleston* reported cases with thickened pleura. *Raymond* accepted the existence of an exudative syphilitic pleuritis. *Sadowski* saw a case of gumma of the pleura; *Renbier, Gerest* and *Wies* observed cases with pleuritis; but the appearances were in no way different from those of other forms of pleurisy. Likewise, in the cases described by *Massia, Rössle* and *Sugai* no characteristic appearances of syphilis are recorded.

18. *Anthraxis and Syphilis of the Lung.*—*Filadoro* and other writers have noted the frequency of excessive anthracosis associated with lung syphilis; particularly in the peribronchial nodes is the anthracosis marked. *Osler* and *Rössle* have also remarked upon the pigmentation in their cases.

19. *Elastic Tissue in Pulmonary Syphilis.*—Many authors agree as to the persistence or even increase of yellow elastic tissue in syphilis of the lung, particularly in the cases of syphilitic sclerosis. The increase is especially marked in the vessel walls.

20. *Syphilis and Tuberculosis.*—The older writers undoubtedly classed many cases of tuberculosis as syphilis. *Mauriac* and *Petaïn* were the first to attempt a differentiation, but the majority of writers emphasize the difficulty attending both macroscopic and microscopic differentiation. *Hertz's* opinion that the gumma of the lung can not be diagnosed macroscopically still holds good with the majority of pathologists today. *Virchow*, on the contrary, said that the macroscopic diagnosis was the only possible way, as microscopically he regarded the tubercle and gumma as having the same appearances. *Birch-Hirschfeld* declared that the only sure method of differentiating was the demonstration of the tubercle bacillus. Other writers insist upon the formation of fibrous connective tissue extending from the hilum along the bronchi and vessels as a certain indication of syphilis, (*Lindwahl, Downing*). The fibrous nature of syphilis is emphasized by many (*Goodhalt*). The occurrence of gummas around the main bronchus is considered by *Massia* as an important sign. According to *Fournier* the characteristics of the gumma are their unilateral occurrence, relative scarcity, nonconfluence, non-transparency and elastic consistence. The microscopic differentiation according to *Ziegler* rests upon the scarcity of giant cells and

the new formation of blood vessels in the periphery of the gumma. According to *Kaufmann* the gumma is characterized by its non-calcification and by the presence of plasma cells. *Fowler* observed calcareous deposits in gumma of the lung. *Stanley* holds that the proliferation of the elastic tissue is greater in syphilis than in tuberculosis. *Hänsemann* considers the formation of granulation tissue as characteristic of syphilis. In general, the main points of differential diagnosis of gumma and tubercle, as obtained from the literature, are the rich vascular formation, the grouping in a mass rather than in small nodules, the scarcity of giant cells, and the infrequency of calcification, together with the preservation of the pulmonary architecture, in syphilis.

As to the etiologic relationships of the two diseases there is a widespread belief that a syphilitic lesion of the lung prepares the way for a tuberculous infection, and aids in its spread. (*Brock, Power, Potter*, etc.). Other writers believe that a tuberculosis also acts as a spur to syphilis (*Schnitzler, Schlecht, Guerin, Gouget*). Other writers believe that this not infrequent combination is purely a coincidence (*Balzer*). According to *Sergent* and *Rindfleisch* syphilis of the lung makes fibrous a secondary tuberculosis. *Leredde* has more recently emphasized the importance of latent pulmonary syphilis in causing sclerosis of the bronchi and thus producing a predisposition to tuberculosis. Many cases of syphilitic lesions of the lung might thus easily escape clinical detection and be covered up by a tuberculosis.

21. *Giant Cells in Syphilis*.—Much discussion has centered about the importance of giant cells as diagnostic factors between syphilis and tuberculosis. Many writers have noted their occurrence in their cases (*Tanaka, Askanazy, Scheib, Patino, Bade*); others have not (*Sugai*); and other writers say that true giant cells do not occur in the syphilitic lesion, but only false giant cells. *Baumgarten* considered the presence of giant cells as meaning always tuberculosis, while *Hause* says they are always present in the lesions of syphilis. Today the majority of writers agree that they occur in both diseases, although usually more abundantly in tuberculous processes; and that there is no difference at all in these cells as found in both conditions.

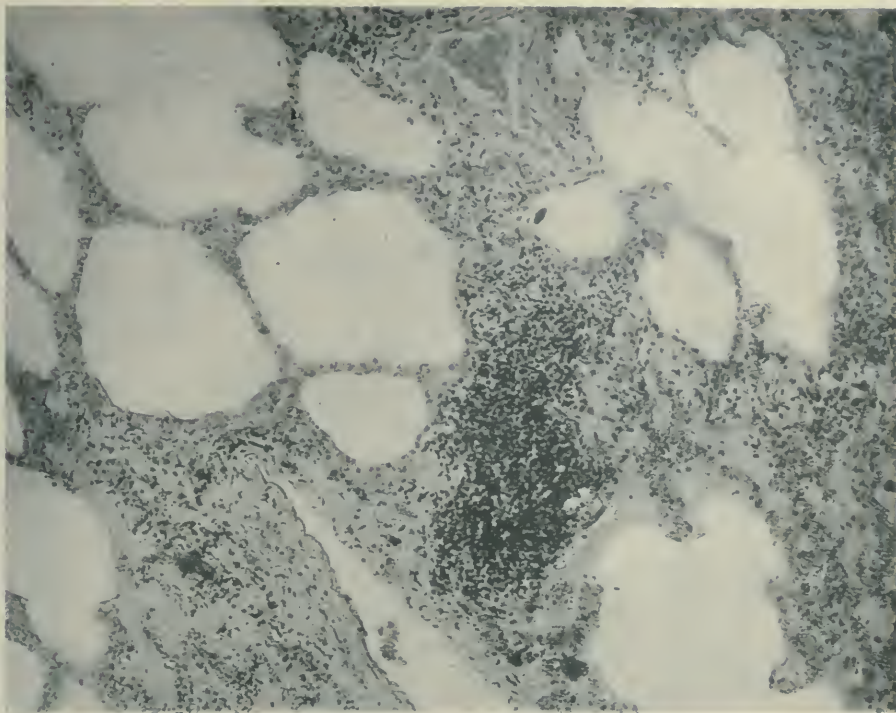


Fig. 13.—Diffuse syphilis of the lung with irregular fibrosis and patches of plasma cell infiltration. In this lung every stage between these small infiltrations and fully developed gummas was found.

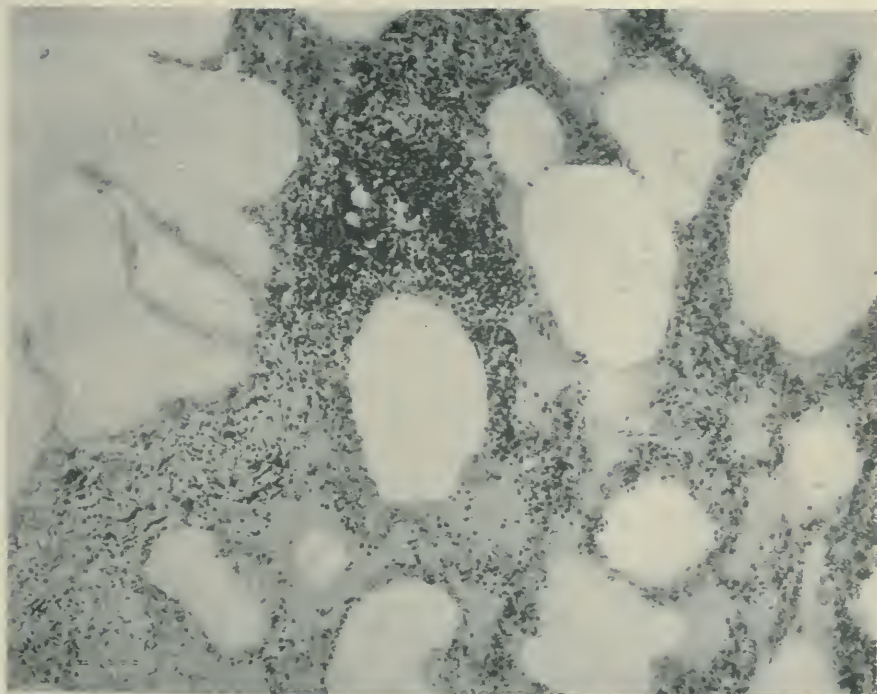


Fig. 14.—Plasma cell infiltrations and fibrosis in active syphilis of the lung.

II. RESULTS OF THE STUDY OF THE LUNGS IN 152 AUTOPSY CASES OF SYPHILIS

From the above study of the literature it will be seen there is very little that is definitely known about syphilis of the lung, aside from the relatively infrequent cases of pulmonary gumma. We know today from the work of *Warthin* that the gumma is a relatively rare lesion of syphilis, and that the essential pathology of syphilis, as it affects the central nervous system, heart, aorta, liver, pancreas, adrenals, testis and other organs, is a mild inflammatory process characterized by lymphocyte and plasma-cell infiltrations, leading eventually to fibrosis and atrophy. Such modern pathologic criteria, together with intensive search for the *Spirochete pallida*, have not yet been applied to the problems of pulmonary syphilis. Undoubtedly the difficulties attending the study of syphilitic changes in the lungs are greater than in the case of other organs, owing to their peculiar structure and the great frequency of other pathologic processes that may obscure the syphilitic process. The most logical way of getting at the matter, it would seem, would be to study thoroughly microscopically the lungs taken at autopsy from syphilitic cases. This has not yet been done, and we do not know to what extent the lung shares in the minute inflammatory changes that occur in the other organs in every case of syphilis examined. At Professor *Warthin's* suggestion I have undertaken such a study of the lung in known cases of syphilis. One hundred and fifty-two cases were selected from the autopsy material of the Pathological Laboratory of the University of Michigan in which an undoubted diagnosis of syphilis had been made from the presence of specific syphilitic lesions in other organs and tissues. These cases included (about one-third) those that had been clinically diagnosed as syphilitics before death, including paretics, tabetics, aortic aneurysms, syphilitic myocarditis, aortitis, hepatic syphilis, gummas of brain, lungs, liver, bones, skin and testis, salvarsan poisoning (5 cases), and other clinical forms of syphilis. The remaining cases were those in which a clinical diagnosis of syphilis had not been entertained in connection with the patient's terminal affection. In these the diagnosis of syphilis rests upon anatomic signs of syphilis alone, or upon a combination of anatomic lesions and the demonstration of the spirochete.

The material was, for the greater part, formol fixed, paraffin imbedded, and stained with various stains, chiefly hematoxylin and eosin, Weigert's elastic tissue method, Kresylecht-violett, Van Gieson's and the Levaditi method. Blocks were taken from the two lungs and from different portions of the lobes; but even with this work the amount of lung tissue examined is relatively very small. Negative findings can not, therefore, be taken as absolutely indicative of all parts of the lung, inasmuch as the areas of active lesions of syphilis may be sharply localized in certain portions, and may be entirely missed. Our experience in searching for active areas in such organs as the heart and aorta has taught us that in some cases it becomes necessary to take many blocks of tissue and cut many thousands of sections before active lesions are found. Much more necessary is this with the Levaditi method in the search for spirochetes. So time-consuming is this that I was able to apply it to ten cases only, making four blocks of each case and cutting the sections at eight different depths. Negative results under such conditions may be wholly the result of the inadequate search.

As the result of this study I found in 12 cases out of the 152 histologic changes in the lungs that I regard as undoubted syphilitic lesions, as follows:

1. Gumma of the Lung	3 cases
2. Syphilitic Peribronchitis with Arteritis	2 cases
3. Syphilitic Fibrosis with Arteritis	4 cases
4. Syphilitic Arteritis	3 cases
<hr/>	
Total	12, approximately 8 per cent.

These diagnoses were made upon the modern histologic criteria for syphilitic lesions as given in the Harvey Lectures for 1915 and 1918 by *Fordyce* and *Warthin* respectively.

Gumma of the Lung.—In one case the diagnosis of pulmonary gumma was made macroscopically by *Warthin* at the autopsy table and confirmed microscopically. There were pleural adhesions, some fluid in the cavity, and a number of pigmented nodules under the pleura. Both miliary noncaseating and larger caseous gummas

were found throughout the lungs. Microscopically, the caseous gummas showed three distinct zones, a central caseous area, an intermediate fibrous zone with many new blood vessels, and an outer vascular, infiltrated zone rich in plasma cells and lymphocytes. In some of the gummas the outer zone is very broad and diffuse, disappearing gradually in the thickened walls of the bordering alveoli, while others have a more discrete border, but never as sharply circumscribed as the edge of a tubercle. The lung tissue at the periphery of the gumma is compressed and pushed away, but does not show any especial characteristics. Rarely do the gummas touch each other and form a continuous mass; they do not become confluent as do miliary tubercles. The tissues surrounding the smaller gummas often show a heavy deposit of anthracotic pigment. The central caseous zone presents the appearance of a coarsely granular caseation in which few nuclei in varying stages of karyorrhexis are seen. The outlines of capillaries containing blood cells and fibrin can still be made out. There is no fibrin presented in the caseous area except in these vessels, in contrast to the fibrin threads so abundantly found in the caseous centers of tubercles. The intermediate fibrous zone is made up either of young fibrous tissue or an older, more hyaline form, but never distinctly epithelioid, as in the tubercle. Fibroblasts appear, and great numbers of angioblasts in the form of cords or young capillaries containing blood cells. This zone usually shows many plasma cells and lymphocytes, and these increase in number in the outer infiltrated zone, which may appear to be made up almost entirely of plasma cells, but capillary proliferation and increase of stroma can always be made out in this zone. The larger blood vessels in part show the picture of syphilitic endarteritis, particularly when the vessels appear to be the starting place of the gummatous process. Other vessels show hyaline change. Many very small infiltrations of lymphocytes and plasma cells, with occasional endothelioid cells occur. There may be very young miliary gummas or simple syphilitic lesions. In some cases it is very difficult to differentiate these, when taken alone, from hyperplastic rudimentary lymph nodes or young tubercles. In some cases it may be impossible to do this, as other writers have affirmed, and the diagnosis rests upon the more completely developed lesion. As such lesions will nearly always be found in connection with the

younger ones, there will practically never be any difficulty in making a differential diagnosis of syphilis. Giant cells exactly like those of tubercles, with peripherally arranged nuclei were present in this case, but not so numerous as is usual in tuberculosis.

The gumma, even the youngest form, is essentially a vascular lesion, built up largely of angioblastic proliferations infiltrated with plasma cells and histogenetic lymphocytes. As the new formed vascular tissue develops, its vessels in part become obliterated or thrombosed, the connective tissue more hyaline, the cellular infiltration less, and at last the older central part caseates. Typical changes appear in the medium and larger vessels of the part, proliferation of the external and internal coats, degenerative changes in the intima and middle coats, with plasma cell infiltration.

In the caseous area the alveolar structure may at times be preserved; yellow elastic tissue may be present, both of the alveolar wall and of the blood vessel walls, although its amount may be reduced. At the periphery the amount of elastic tissue may be increased in places, in others it may disappear; the fibers may be short and thick as in degenerating elastic tissue. In some gummas the elastic tissue may disappear entirely in the caseous zone, and no elastic tissue appears in the new formed vessels. Around some vessels the elastic tissue appears degenerated, forming irregular masses staining poorly. In some of these areas there is a proliferation of spindle cells infiltrated with small cells. In general the elastic tissue is better preserved than in tuberculosis. Some vessels show a collagenous degeneration. The epithelial proliferation in the alveoli described by some authors was not present in my case. A striking difference from tuberculosis is shown in the gradual transition of the lesion to the neighboring tissues. The scars of the healed gummas are very characteristic. They are never round, but have an irregular form with extensive ramifications, and are vascularized. Around the borders of the recent scars remains of the syphilitic infiltration may still show. Staining for spirochetes negative. Patient had clinical history of syphilis.

In the other two cases of pulmonary gumma the diagnosis was not made macroscopically, one of them showing small noncaseating gummas, the other gummas in the stage of cicatrization. The first of these cases showed the same microscopic pictures as did the smaller gummas in the case just described. Giant cells were pres-

ent. There was an extensive zone of fibrosis beneath the pleura. This showed lymphocyte infiltration with abundant anthracosis and scattered miliary gummas. The tissue showed much new formation of blood vessels. Zones of vascularized fibrosis started beneath the pleura and extended through the lung. In these connective tissue trabeculae remains of the syphilitic infiltration are present in areas. No mast cells were found in these infiltrations. Yellow elastic tissue was absent in the fibrosis. The smaller vessels showed no syphilitic changes. Tissues from this case were not stained for spirochetes.

The third case of healing gumma coincident with a hepar lobatum showed the same essential histologic picture as in the first case. Masses of sclerotic tissue surrounded some of the bronchi; this contains in many places remains of the syphilitic infiltration, and small nodules of plasma cells (miliary gummas). The scar of the large healing gumma is stellate, showing a peripheral plasma cell infiltration, vascularization and pigmentation characteristic of the gummas in the other two cases. Through the scar some elastic fibers can be found; at the border they are more abundant and occur in groups of fibers, in some cases preserving the contour of the vessel wall. The larger blood vessels show syphilitic arteritis. In some of the bronchi surrounded by sclerotic tissue there is a marked proliferation of the bronchial epithelium, almost obliterating the lumen. This case was not stained for spirochetes.

Syphilitic Fibrosis of the Lung.—A very marked fibrosis was found in 18 cases out of the 152; a well marked condition of brown induration was found in 43 cases; while an increase of connective tissue associated with chronic passive congestion was present in 124 cases, or 82 per cent. These findings are very striking, and are in general accord with the changes produced by syphilis in other organs (fibroid heart, arterial sclerosis, chronic interstitial pancreatitis, chronic fibroid orchitis, etc.). The question, of course, is to what extent this fibrosis is the result of the direct localization and action of the spirochetes in the lung tissues, or how much of it is purely secondary to the damaged heart and its enfeebled action. Are these lungs showing an increase of connective tissue the seat of a syphilitic inflammation, or is the fibrosis the result of a chronic passive congestion? Are these lungs purely cardiac lungs?

At the beginning we must insist upon the fact that the fibrosis due to syphilis takes its inception in a typical inflammatory process due to the local action of the spirochetes; and *unless this infiltration is shown we can not make a positive diagnosis of syphilis.* Fibrosis is the termination, the sequel, of the syphilitic process, and it is only the active area of inflammation that presents specific characters by which we can diagnose it positively, although certain characteristics of the syphilitic scar may at times aid greatly in the diagnosis. *From the syphilitic inflammatory infiltration proceeds a fibrosis which should extend along the vessels and bronchi as well.* The syphilitic process may, however, be masked by other processes (tuberculosis, pneumonia, gangrene, etc.).

The connective tissue formation in the lungs of 60 cases of tuberculosis was studied in comparison with the syphilitic lungs. This study convinces me that it is never impossible to distinguish the fibrosis of tuberculosis from that of syphilis, no matter how difficult the case may be. The earliest lesions of pulmonary syphilis may escape our notice more easily than the early tubercle; and there can be but little doubt that many syphilitic lesions of the lung do escape our notice pathologically. The formed gumma and the developed tubercle can be readily distinguished by the vascular, closely packed, epithelioid, sharply circumscribed, conglomerating character of the latter, while the gumma appears as a more loosely arranged, less sharply delimited, vascular granulation tissue, scant in epithelioid and giant cells, and infiltrated with lymphocytes and plasma cells. The scar of the tubercle is round, sharply delimited, with concentric fibers, hyaline, scant in neuclei, devoid of vessels and elastic tissue, less given to anthracotic pigmentation, but more frequently calcified, and very often confluent or conglomerated. The scar of syphilis is irregularly radiating or stellate, not sharply delimited, more like ordinary cicatricial tissue, still contains blood vessels, often with angiectatic capillaries, continuous with the thickened walls of the nearest alveoli, still shows elastic fibers, and the outlines of old vessels and alveolar walls; the scars of gummas are extremely rarely conglomerated or confluent; the syphilitic fibrosis begins under the pleura and around the bronchi, and is more frequently anthracosed, and very rarely calcified. But the most conclusive differential point is the finding in the fibrosis of syphilis of col-

lections of plasma cells; and such active areas are probably as frequent in syphilitic fibroses of the lung as they are syphilitic processes elsewhere in the body.

Likewise, the syphilitic lesions of the vessels, when found, are so typical that they alone will fix the diagnosis. I have to state here that I do not agree with many of the text book pictures of syphilitic arteritis in the lungs, as the conditions pictured may exist in the absence of syphilis. Although some writers say that a differential diagnosis can not be made between the vascular changes in pulmonary tuberculosis and those in pulmonary syphilis, I am convinced that such a differentiation can be made. In tuberculosis the endarteritis and the periarteritis are of one character; all three coats of the vessel are attacked in a massive way, while in syphilis the middle coat may show no alteration. This is in opposition to *Lindwahl* who states that in syphilis all three coats of the vessel are attacked massively. I hold that this is not true of the syphilitic process. The proliferation of the intima and the obliteration of the lumen may be alike in some cases; the vessel lumen may be obliterated by the pressure of a gumma, as well as of a tubercle. The descriptions in the text books of the obliteration of the lumen by its being pushed to one side by proliferation of the internal coat are typical of syphilis. In tuberculosis no coat of the vessel is respected; in syphilis the vessel may show an intact middle coat. The infiltration of the inner coat by round cells is most marked in syphilis and the elastic tissue is better preserved; proliferation of elastic tissue takes place in the internal coat in syphilis and not in tuberculosis; the middle coat is better preserved and its muscle often hypertrophic and well differentiated. In tuberculosis the elastic coats disappear or are degenerated, and the muscle fibers of the middle coat may disappear or show atrophy or degenerative changes. Cellular infiltration of the middle coat means syphilis; if the adventitia shows plasma cell formation, new capillaries and new formed elastic tissue, the process is syphilitic. Tuberculosis causes massive changes in the vessels from the outside; syphilis coat by coat regularly. Hyaline change in the smaller pulmonary vessels may occur in either process.

Still more difficult is the differentiation of syphilitic fibrosis and that of chronic passive congestion, particularly the more severe forms of brown induration. It must be borne in mind that *Virchow*

and other writers have considered brown induration and the heart lesion cells as syphilitic lesions. It is a striking fact that 28 per cent of our autopsy cases have shown a typical brown induration of the lungs, and 82 per cent have shown the pulmonary changes of chronic passive congestion. In comparison with these cases we examined the lungs of 100 successive autopsy cases that showed no lesions of syphilis and found only 5 per cent showing this lesion. Nothing could better illustrate the effects of syphilis upon the heart and the secondary results upon the lungs. The coincidence of the brown induration, the typical heart-lung, is due to the fact that can not be too often repeated that syphilis is the most important etiologic factor in cardiac disease. Therefore, if an autopsy case shows a well-marked brown induration the chances are greater for its association with syphilis than with any other condition.

The general appearances of the fibrosis of brown induration and of syphilis are very much alike; the existence of the anthracotic border is common to both. The essential differences rest in the typical vascularization and infiltrations of syphilis. In the connective tissue of syphilitic fibrosis the small diffuse or focal collections of lymphocytes and plasma cells, with or without typical gumma formation, and associated with characteristic vascular changes make possible the differential diagnosis. The vascular changes due to the chronic passive congestion, dilatation with hypertrophy of the coats, and often hyaline change, may in part obscure the syphilitic vascular changes. Even in the combination of syphilis, tuberculosis, and brown induration the differential points can be found on careful search. The fibrosis of brown induration follows the vessels, radiating from the hilum; it is more regular than that of syphilis, and does not show the stellate radiations characteristic of the latter. So far as the fibrosis is concerned the yellow elastic tissue stain offers no aid in the differential diagnosis of syphilis and brown induration; but it does in the case of the vascular changes. In the nonsyphilitic cases no infiltration is found at the periphery of the vessels. The occurrence of connective tissue bundles outside of the vessels, their vascularization and evidences of plasma cell infiltration are the essential diagnostic points by which the fibrosis of syphilis may be distinguished from that of chronic passive congestion. As practically

every lung of syphilitic fibrosis is also a lung of chronic passive congestion, the differential diagnosis requires a thorough and careful histologic study for the determination of these points. If the syphilis is active the diagnosis may be easily and quickly made, but in old latent cases extensive search may be necessary to locate characteristic lesions.

The presence of the cuboidal cells of *Tripier* does not favor the diagnosis of syphilis, as they are found in any chronic fibroid process in the lung (tuberculosis, actinomycosis, chronic fibroid pneumonia, etc.). Further, the idea quite commonly held that the folding in of the elastic tissue coats in the vessels is a sign of syphilis is not correct. This lesion is not confined to syphilis, but may be found in sclerosis due to other causes. Aside from the characteristic infiltrations of the vessel wall the good preservation of the middle coat is a feature confined to syphilis. The classical descriptions of syphilitic arteries in the text books no longer apply, in as much as nonsyphilitic cases may show the same changes. It is possible to regard as syphilitic only those vascular changes described above. The classical splitting of the elastic coats is not confined to syphilis; endarteritis without the cellular infiltration of the vessel coats is not syphilitic. Proliferation of the elastic coat inside the internal elastic is not characteristic of syphilis. Blood vessels with typical syphilitic infiltrations show little change in the elastic tissue. The increase or hypertrophy of the muscle of the vessels does not take place in syphilis at all, or to a degree so slight that it is not recognizable. In brown induration such muscle changes are marked in the vessels.

Pleura in Syphilis of the Lung.—While chronic adhesive pleuritis, old pleural adhesions and thickenings were common findings in these cases, no characteristic changes of syphilis were found in the pleura.

Bronchial Lesions in Syphilis.—Typical active syphilitic peribronchitis was found in two cases. In one case associated with marked syphilitic lesions of the brain, aorta, heart and testes, the peribronchial tissues showed a beautiful plasma cell infiltration, with new-formed vessels, formation of a vascular connective tissue around the infiltration, with heavy deposits of anthracosis. In many places the infiltrations are nodular (miliary gummas). The bronchial epithelium is well preserved. The alveolar walls showed nothing characteristic. Patches of sclerosis occurred

throughout the lungs. In the peribronchial connective tissue spaces lined with the cuboidal cells of Tripier were present. The vessels showed a typical syphilitic picture, with plasma cell infiltrations in intima and adventitia. New-formed muscle occurs in connection with the bronchi, but not in the vessels. The elastic tissue of the bronchus is either destroyed or pushed away at the seat of the infiltrations, often appearing on the outside as thick, short, broken fibers, or as bundles of new-formed elastic fibers. These changes affected all parts of the two lungs. One lobe showed the condition of a gray hepatization of croupous pneumonia, the immediate cause of death. No spirochetes were found in the lung.

In another cause the lung showed marked sclerosis of the blood vessels with proliferations of the intima not of the syphilitic type, but with typical syphilitic infiltrations of the inner and outer coats. Typical syphilitic infiltrations existed around the bronchi with new-formed muscle and connective tissue. The muscle coats of the bronchi were greatly thickened, and the cuboidal cells of Tripier were found in peribronchial spaces. Scattered areas of vascularized granulation tissue infiltrated with plasma cells occurred throughout the lungs, particularly beneath the pleura at the lung borders.

In no other cases were typical syphilitic lesions of the bronchi found, although the latter showed frequently various conditions that different authors have regarded as due to syphilis. We were not able to find syphilitic changes in the lungs associated with bronchiectasis. Tripier's cuboidal cells occurred in many cases without syphilitic changes being found. My experience is different from that of *Rössle* who so frequently found remains of infiltrations in sclerotic peribronchial tissues. In these cases no evidence of congenital pulmonary syphilis was found that could be recognized as such except in two cases in which other organs also showed the lesions of congenital syphilis. These cases did not show the proliferation of alveolar cells described by *Rössle*. The differential points between congenital and acquired pulmonary syphilis in adults, as given by *Rössle* do not hold. The differential point as to the anthracotic border around the congenital areas does not hold; and it is impossible in the adult to distinguish between congenital and acquired pulmonary syphilis.

Mucous Glands.—No changes were found in the bronchial mucous glands.

Lymph Nodes.—In one case, associated with marked syphilitic mesarteritis of the large pulmonary arteries with aneurysm of a main branch in the upper left lobe the peribronchial lymph nodes showed marked typical syphilitic vascular formations and thickenings, with plasma cell collections. Spirochetes were found in the artery, the aneurysm wall and the peribronchial infiltrations in this case.

SUMMARY

The study of the lungs of these 152 cases gives us 12 cases diagnosed positively as syphilis upon the criteria described above. The cases fall into two groups: 1. Gumma, with peribronchial lesions and arteritis, five cases falling into this group, three of them in the first subdivision; 2. Fibrosis and arteritis, embracing seven cases, three showing definite syphilitic processes in the vessels alone.

If we compare these findings of active syphilitic lesions in the lungs with those found in the other organs of the same cases we are struck by the great disproportion. The heart and aorta of every case showed typical active infiltrations, the testes of every male showed the same, the great majority showed active lesions in pancreas, adrenals and liver, and those cases in which the central nervous system was examined showed a high incidence of syphilitic lesions. Upon what grounds does the apparent greater freedom of the lungs from such lesions rest? Is the lung actually more immune to syphilis and less frequently involved in the mild inflammatory processes that are always found in other viscera? I do not think so; it is very probable that many other lungs were syphilitic, but the specific active changes were not found; and it is only upon these that we can make a positive diagnosis of syphilis. The examination made is, of course, very incomplete; only a limited amount of lung tissue was routinely preserved from the autopsies, and it was possible to examine only a small part of this tissue. The portions examined represent a very small area of the lungs as a whole; and the chances of missing such changes as are produced by syphilis are infinitely greater than of finding them. Further studies of this kind, much more intensive as to the amount of lung tissue examined, are needed before we can pass judgment upon the importance and

frequency of syphilitic lesions in the lung. It seems most probable that the lungs are involved in the mild general infection of syphilis to about the same degree that the other organs and tissues are. The gumma may be infrequent, as it is in all organs, or even rarer, or it may be infrequently diagnosed, both in life and at the autopsy. What this research does show are the facts that the essential lesions of syphilis in the lungs are the same as elsewhere; and, what is extremely important to the clinician, that the lungs of the syphilitic are not normal organs. Our 152 cases of syphilis show the following conditions:

1. Chronic Passive Congestion (Well-marked)	124 cases.
2. Marked Brown Induration	43 “
3. Marked Fibrosis Without Brown Induration	18 “
4. Hemorrhagic Infarctions	28 “
5. Pulmonary Thrombosis	14 “
6. Edema of the Lungs	35 “
7. Atelectasis (Subpleural)	16 “
8. Bronchopneumonia	45 “
9. Tubercles (Of Clinical Importance)	21 “
10. Excessive Anthracosis	61 “
11. Emphysema	42 “
12. Chronic Pleuritis	19 “
13. Bronchiectasis	6 “
14. Presence of Corpora Amylacea	6 “
15. Pulmonary Gangrene	6 “
16. Fibrosis of Peribronchial Nodes	2 “

A terminal bronchopneumonia or croupous pneumonia occurred in a very high per cent of the cases in connection with an inadequate heart. It is, of course, impossible to state how much of the pulmonary pathology so strikingly shown in this series of cases is due primarily to syphilis of the lung tissue, or secondarily to the effects of syphilis upon the myocardium. A vicious circle will sooner or later be produced, as far as the lungs are concerned. To any primary damage produced in these organs, there will sooner or later be added a chronic passive congestion due to the myocardial lesions. To what extent does this modify the syphilitic process? We can not say now. At any rate the great majority of autopsy cases of syphilis show lungs having a greater or less degree of

fibrosis, as do the other organs and tissues, and with this fibrosis they present a varied pathologic picture.

CONCLUSION

The diagnosis of pulmonary syphilis must be made microscopically. The lungs of syphilitics show an incidence of fibrosis comparable with that observed in other organs of the same cases. They show also a high percentage of pulmonary pathologic conditions, in part, at least, referable to the coincident myocardial affection. A certain number of cases (here 12 out of 152) present a specific syphilitic pathology of clinical importance, in the form of gumma, fibrosis, peribronchitis and arteritis. To what extent the high incidence of fibrosis of the lungs is due to syphilis alone can not be decided now, but it is probable that the lung is not exempt from involvement in the mild inflammatory process caused by syphilis in other organs, and which lead eventually to fibrosis.

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SOME PRACTICAL CONSIDERATIONS WITH REGARD TO SYPHILITIC AORTITIS

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I DO not pretend to be a syphilologist, but it has fallen to my lot to diagnose a goodly number of cases of syphilis of the circulatory system and also treat a fairly large proportion of them. Out of my experience certain points of practical importance have impressed themselves on my mind which may be of interest to the readers of this journal and which I propose to set down herein. They are not novel or original, yet although frequently expressed by writers, they do not seem to have become strongly enough impressed on the minds of some medical practitioners. As the recital of cases seems to carry more weight oftentimes than do mere statements unsupported by case records it has been decided to give the essential facts of a few cases in my experience.

CASE 1.—Mr. C. first consulted the writer in 1896 because of annoying irregularity of his heart action. The examination revealed nothing to indicate organic cardiac disease, and the man was comforted with the assurance that the arrhythmia was simply functional and would disappear upon correction of some obvious digestive disturbance.

Some six or eight years later this patient reappeared complaining of pain in the chest on the right side, and it required no expert examination to make out a saccular aneurysm of the ascending limb of the aorta, shown by a soft pulsating tumor in the second and third right interspaces close to the sternum, as well as by hypertrophy of the left ventricle and a characteristic aortic regurgitant murmur.

The man was informed of the gravity of the condition and advised to go to bed on a restricted diet in the hope of promoting a clotting of blood within the aneurysmal sac. This regime was carried out faithfully for a number of months with only moderate success. So far as clinical examination could determine, the aneurysm did not increase appreciably in size.

I had already become convinced that aortic aneurysms were of syphilitic origin and this patient was so informed. His rejoinder was an emphatic statement that he had never had a chancre. He frankly admitted gonorrhea and stated he would admit syphilis if he had ever contracted it. Not at all convinced by this emphatic assurance I had a Wassermann test of the blood made and as was expected this

showed strongly positive. Thereupon was begun an energetic course of mercurial treatment by means of intramuscular injections of the bichloride and by thorough inunctions. The effect was truly surprising and the first result was the disappearance of his pain which up to that time had not yielded to potassium iodide or to his prolonged rest in bed and restricted diet. And here it may be stated the pain has never recurred. The second result was a distinct hardening of the projecting aneurysm, so that instead of being so soft and yielding as to make one dread lest even slight pressure should cause it to rupture, it now is firm and after a lapse of more than a dozen years shows very little if any increase in size and gives no symptoms of pressure on the internal structures. In fact the man feels entirely well.

This patient has never received salvarsan but has been most persistent and faithful with mercurial treatment both in the form of injections and inunctions, resorting to the latter several times yearly for periods of six to eight weeks. It is to the thoroughness of his medication that his present good condition is owing. In addition he has refrained from forms of exercise that would be likely to overstrain his heart or dilate his aneurysm.

CASE 2.—Mr. D., a machinist, has been under observation and periodic treatments by mercurial injections and rubs for perhaps three years. In addition he has received two courses of salvarsan, five injections in each series. He admitted luetic infection some twenty years ago and shows pronounced signs of mesaortitis with the characteristic finding of aortic regurgitation but no visible or palpable aneurysm. When first coming under treatment he would experience anginoid pain on hurried walking and was annoyed by attacks of palpitation. He now experiences only very slight pain in the upper chest on hurried walking and in September last was able to march in a Knight Templar parade. This man's present good health is likewise attributable in the main to the faithfulness and thoroughness of his antiluetic treatments.

CASE 3.—Mr. O. has been under observation and treatment for at least three years, having received two or three series of salvarsan injections yearly beside a thorough course of mercurial injections and rubs every few months. He first sought advice because of persistent tachycardia with occasional attacks of palpitation. The heart showed no obvious organic change, but as he had darting pains in the lower extremities with absent patellar reflex and a slight Argyll Robertson pupil he was referred to a colleague for a spinal puncture and examination of the spinal fluid. This confirmed the diagnosis of a beginning tabes dorsalis and a vigorous treatment was begun as mentioned above. Repeated heart examinations were made and at one time signs were detected that indicated slight left ventricle dilatation and as was thought, beginning aortitis. He was given digitalis for some weeks with benefit though without slowing down the heart. At the present writing the heart is distinctly improved in both physical findings and rate and all signs of his tabes have disappeared. He feels and appears perfectly well but intends to resort to treatment from time to time with untiring faithfulness.

CASE 4.—Mr. B. was examined originally some ten or twelve years ago when he sought advice because of persistent and annoying tachycardia with intermittence

due to ventricular extrasystoles. Examination of the heart disclosed no obvious organic defect and there being no discoverable etiologic factor in indigestion or habits he was questioned in regard to possible syphilis. This was frankly admitted and the man was referred to a specialist for diagnosis and treatment. The blood test was positive and he was given a thorough course of salvarsan with the result at length that the Wassermann was negative. This finding seemed to satisfy the man, for after the syphilologist had dismissed him he did not come before the writer for several years.

When at length he reappeared it was on account of a recurrence of disturbed cardiac action. Although the heart findings were not very distinctive it was believed that the myocardium had suffered from the luetic infection and treatment by mercury, digitalis, and rest was instituted. Improvement occurred, but from that time to this occasional returns of symptoms have been noted.

For the past three years it has been difficult to get this man to persist in energetic specific medication and for the reason that he declares he feels well. Nevertheless a faint aortic systolic murmur has developed with a moderate increase in the area of deep cardiac dullness at the left and an occasional systolic whiff at the apex, proving it is believed that the heart muscle has not escaped damage. So long as this patient takes his digitalis and subjective symptoms are kept in abeyance he seems to be content. Notwithstanding, I believe there is danger ahead for this man and mainly because he will not tackle his underlying infection vigorously and faithfully, as have done those whose cases have been briefly described.

Warthin has shown most convincingly how great is the predilection of the *Spirocheta pallida* for the heart and aorta and that he has been able to detect the organism in these structures even after what was thought to be energetic specific medication. How great, therefore is the error for a person with lues to fancy himself safe after the disappearance of objective and subjective symptoms. He is like the ostrich that hides its head in the sand and thinks itself safe. The watchword for all syphilitic patients should be eternal vigilance.

Numerous instances could be cited of the recognition of aortic syphilis without resort to a blood test and hence the following points may be mentioned. (1) If a person either male or female in the late thirties, early forties or still later in life furnishes signs of aortic regurgitation minute inquiry should be instituted regarding the etiologic factor, and if no evidence can be found of previous streptococcus infection, as inflammatory rheumatism, tonsillitis, scarlet fever, etc., suspicion should attach at once to the likelihood of syphilis. (2) The patient's denial of a chancre should not be considered sufficient, especially if gonorrhea is admitted, as witness

the first case in this paper. (3) Not infrequently it will be learned on close inquiry that the aortic regurgitation has appeared within the last few years and that the man may have been accepted for life insurance five or ten years previously and that no streptococcus infection occurred in the meantime. (4) Careful percussion over the sternum generally detects more or less dullness of the manubrium extending into the first interspace at either side, while the subclavian arteries often pulsate visibly above the inner and middle third of the clavicles. (5) There is rarely a palpable systolic thrill in the aortic area at right of the sternum, but a perceptible systolic impulse may be felt, and generally a distinct to and fro murmur replaces the two aortic tones. (6) Whereas in some instances of pronounced insufficiency of the aortic valves from inflammatory rheumatism similar findings are found it is likely that signs of aortic dilatation are less pronounced while one of the aortic tones may be heard as well as the murmur and frequently there is a systolic thrill.

As is well known, syphilitic aortitis leads sooner or later to dilatation of the arch and consequent stretching of the ostium and regurgitation. Regurgitation may not necessarily attend a sacular aneurysm, but such instances are rare as compared with those cases in which leakage does take place. Given the above points in a man of forty or over, the chances are in favor of a syphilitic mes-aortitis, and yet be it remembered this is not limited to the male sex, as I can testify from instances in my own experience.

Finally, I desire to emphasize most strenuously the necessity of the most vigorous antisymphilitic treatment in all such cases. I believe that thorough mercurial medication whether with or without salvarsan should be resorted to from time to time practically for the rest of the patient's life even after reliable blood tests are declared negative. The damage done the heart and aorta can not be repaired and possibly the spirochetes in the tissues may not be reached, but the beneficial effects of prolonged and oft-repeated treatments by means of mercurial rubs and injections (not by the oral administration of mercury or iodides) have been demonstrated in so many of the writer's cases that he would offer this as the one practical consideration of this commonplace communication.

SYPHILIS OF THE GREAT VESSELS

By A. F. TYLER, M.D., OMAHA, NEBR.

(Received for publication, November 24, 1919.)

SYPHILIS of the great vessels is so closely linked up with aneurysm that the discussion of one is practically a discussion of the other, so that in this paper we shall think of aneurysm as an end result of syphilis of the vessels, excluding of course, traumatic aneurysm.

The percentage of aneurysm in nonsyphilitic patients is so very small that it is almost negligible. The literature of this condition dates back to about 200 A.D., when Galen first described aneurysm, differentiating between the traumatic type and the ordinary idiopathic dilatation. At that time, of course, the causative factor was not definitely known but later this cause became known and so every patient in which an aneurysm is found is considered to have had previous syphilitic infection unless otherwise proved.

TYPES

There are a number of types of aneurysm, the ascending arch of the aorta being the most frequently involved. Out of a large number of cases which have been collected from the literature, that part of the aorta above the diaphragm was affected with 75 per cent while 25 per cent of the aneurysms were found below the diaphragm. Of the 75 per cent which occurred above the diaphragm, 60 per cent originated in the ascending portion of the arch. The most frequent type of the ascending portion of the arch is the sacculated aneurysm. Of the descending arch and thoracic aorta, the fusiform aneurysm is the most common. Some one has said that aneurysm of the ascending arch of the aorta is essentially syphilitic, while that of the remaining portion of the thoracic aorta is more apt to be arteriosclerotic. This has been true in my observation. In fact, I have yet to find an aneurysm of the ascending arch in which there has not been either a history of venereal infection or a positive Wassermann. On the other hand, there have been a number of cases under my observation of fusiform dilatation of

the thoracic aorta or of the descending portion of the arch of the aorta in which the Wassermann test was negative. The pathology found in syphilitic aortas, where dilatation has taken place of course, is that of the syphilitic plaque followed by a weakening of the wall and a bulging of the wall so that an irregular dilatation takes place. The sac of the aneurysm is made up of the intima and the adventitia, the media not being present. This is due to the fact that the media has ruptured under pressure from within and the more tenacious inner and outer coats withstand the stretching.

The sacculated type of aneurysm is usually found in the ascending portion of the arch. When this is small the blood enters and leaves the sac, but as the sac becomes larger, there is usually more or less clotting of the blood within the sac and later this clotting may become organized so that there will be little, if any, of the blood circulating through that part of the aorta entering into the aneurysmal sac. This pathologic condition is of importance, especially as connected with the diagnostic findings which we shall mention later. This type of aneurysm is usually just above the sinuses of Valsalva. One case came under my observation a number of years ago in which the aneurysm involved the sinuses of Valsalva and was accompanied by a rupture into the pericardium. This rupture was the first intimation to the patient that he had any serious trouble. This case was diagnosed by the clinician, A. D. Dunn, previous to death, the blood being aspirated from the pericardium. After the aspiration and medical treatment, including antisyphilitic treatment pushed to the limit, the patient continued in fair condition of health for two years when he suddenly died. The diagnosis was proved at postmortem. As the sac of the aneurysm involving the ascending portion of the arch continues to enlarge it usually extends out to the right and slightly forward but more posterior. The sacculated aneurysm involving the transverse portion of the arch is more apt to cause an erosion of the sternum from pressure than that of the ascending portion of the arch. The majority of these extend backward, but a small percentage press against the sternum. Aneurysm of the descending portion of the arch follows the path of least resistance and is found extending to the left and posterior.

INCIDENCE

Aneurysm is found much more frequently in males than in females, probably due to the fact that they carry on more strenuous vocations and are more frequently infected with venereal disease. The large majority of aneurysms occur in mature life during the fourth and fifth decades.

SYMPTOMS

The aneurysm of symptoms grows from the transverse arch of the aorta while the aneurysm of physical signs springs from the ascending portion of the arch. This is an old aphorism but it is abundantly proved by experience. The patient is usually brought to the physician because of a dyspnea or a nonproductive cough. Aneurysm of the descending portion of the arch of the thoracic aorta will sometimes produce an erosion of the vertebræ. In this type of aneurysm the patient may be brought to the physician because of pain. This is a late symptom of course, and is not one of good omen. Some patients suffer from a hemorrhage of the throat due to the venous congestion from pressure of the sac upon the esophagus or trachea and rupture of these varicose veins inside the esophagus. The nonproductive cough is caused either by pressure on the trachea or because of an associated bronchitis.

PHYSICAL FINDINGS

First, inspection. There may possibly be an abnormal pulsation on either side of the sternum. This would be due to a dislocation of the heart, deformity of the thorax or retraction of the lung. This pulsation, if observed, is usually above the level of the third rib and to the right of the sternum. In advanced cases of aneurysm of the transverse arch with erosion of the sternum, a pulsatile tumor will be observed over the sternum. The skin over this will be thin and often blood-stained. Occasionally the apex beat will be to the left of the nipple line because the heart is dislocated slightly, extending farther to the left than normal. This is rarely the case as aneurysm of the aorta is seldom accompanied by enlargement of the heart. The elongation of the aorta which takes place causes the heart to assume a transverse position within the chest cavity. This position usually accounts for any misplacement of the apex beat.



Fig. 1.—Photograph of patient suffering with sacculated aneurysm of the transverse arch of the aorta which projects forward and produces erosion of the sternum. The sac of the aneurysm was subcutaneous. Pulsation was plainly visible and was easily felt and heard. The patient had known that this was present for more than three years.



Fig. 2.—Photograph of sacculated aneurysm of the ascending arch of the aorta made from the postmortem specimen. Death due to rupture of the sac as shown in the illustration.



Fig. 3.—Roentgenogram of patient suffering from sacculated aneurysm of the ascending portion of the arch of the aorta. This is the patient whose complete history is given in the article.

PALPATION

When the aneurysm is deep-seated and within the chest cavity, palpation will usually reveal little. If the aneurysm is springing from the transverse arch, one may be able to detect a thrill. This will usually be systolic in time and will be accompanied by a definite diastolic shock. Palpation will also reveal whether there is a trachial tug present.

PERCUSSION

In the small or deep-seated aneurysm of the thoracic portion of the aorta, little is gained by percussion. If the sac becomes large and involves the ascending portion of the arch, one will get a broadening of the aortic area of dullness extending to the right of the sternum. If the descending portion of the arch or the thoracic aorta is involved the increase in aortic dullness will be toward the left. Often this is best detected posteriorly, especially when in the thoracic aorta.

AUSCULTATION

There may be no auscultatory findings. This is due either to the fact that one is dealing with a deeply-seated lesion, or due to the fact that there is a large sac which has become filled with an organized blood clot so that the blood stream does not enter into the sac, producing little sound. There will usually be a ringing, accentuated aortic sound. There will be a slowing of the pulse in the arteries beyond the aneurysm and those involved in the sac.

X-RAY FINDINGS

The x-ray when used in conjunction with and as an aid to the other means of physical diagnosis has been of great help, especially in making a positive diagnosis of aneurysm of the aorta. The fluoroscopic image should be used in conjunction with the study of properly made x-ray plates. When viewing the chest in which one is suspicious of some vascular disease it is well to study the chest for a considerable period of time in different positions. My custom is to make a general survey of the chest directly from in front, then to focus down upon the heart and aorta. If there is an increase in the width of the aorta, one can know in which direction

this increase extends and can see whether there is definite pulsation. Then the patient should be turned with the rays passing through in the right oblique position so as to determine whether the increase in the aortic shadow is definitely connected with the great vessels or due to a tumor within the mediastinum. Then the patient should be turned to the left oblique position to see whether the ascending, transverse, or the descending, portion of the arch, or whether the thoracic aorta is the site of the disease. The plates,

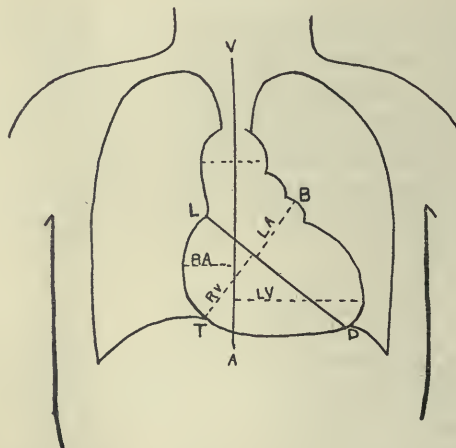


Fig. 4.—Drawing after Groedel showing method of estimating heart size.

L-D, longitudinal diameter.

B-T, diameter through base of heart.

RA, right auricle.

LV, left ventricle.

RA plus LV gives the transverse diameter of the heart.

V-A line drawn through spinous processes of vertebræ used as a base line in measuring the transverse diameter.

In using this method the plate should be six feet away from the anode of the x-ray tube, the patient standing with front of chest against the plate. Exposure should be long enough to catch heart in diastole.

of course, will give us definite information as to whether there is an erosion of the sternum or vertebræ because they are more reliable for this information than is the fluoroscopic image.

DIFFERENTIAL DIAGNOSIS

Aneurysm of the aorta must be differentiated from enlarged heart and aortic insufficiency. Since the heart is enlarged in less than half the cases of aneurysm of the aortic arch, one must always be on guard in making a diagnosis of aneurysm when an enlarged



Fig. 5.—Roentgenogram of patient suffering from aneurysm involving the sinuses of Valsalva which ruptured within the pericardium, filling the sac. Typical water bottle shape of shadow. Blood aspirated from pericardium. Diagnosis made autemortem.

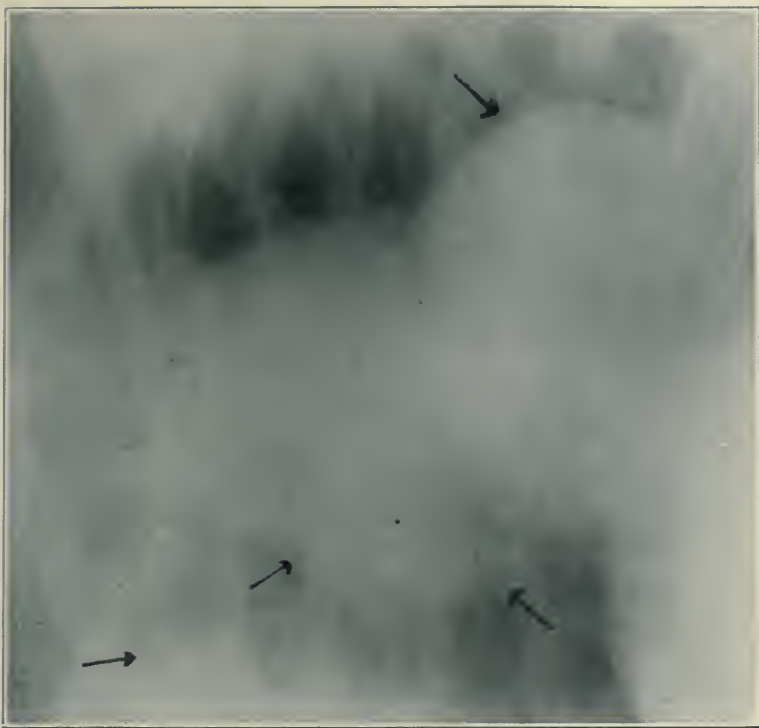


Fig. 6.—Roentgenogram of patient suffering from sacculated aneurysm of ascending portion of aortic arch. Note the transverse position of the heart with round left ventricle. Note hazy condition of right upper lobe of lung, probably a syphilitic infiltration of the lung.

heart is found. The aneurysm must be differentiated from a simple dynamic pulsation of the aorta, which is more pronounced in some patients than in others. One of the most frequent errors in diagnosis is when there is a dislocation of the heart due to a curvature of the spine. The physical and x-ray findings in this condition are very deceiving, unless one looks very carefully and is very thorough with his examination. Another frequent source of error is in the solid tumor of the mediastinum. One, of course, would not expect to see pulsation in a solid tumor, but it has been my observation in a number of cases that the pulsation of the aorta may be transmitted to the tumor mass so that one really observes movement of the tumor mass which corresponds to the beat of the heart. In differentiating tumor from aneurysm I have found considerable help by having the patient swallow a little opaque material which will show the path of the esophagus and show whether the tumor involves the esophagus or whether there is simply pressure against it. Another source of difficulty in differentiating aneurysm from tumor of the mediastinum is found when the sac has become filled with an organized blood clot. In this type no pulsation will be observed. One must differentiate aneurysm from pulsating pleurisy and from tuberculosis of the spine with an accumulation of tuberculous detritus.

PROGNOSIS

Prognosis in large aneurysms is, of course, very grave, fatal termination usually taking place from twelve to twenty months after recognition. Occasionally one will see an advanced aneurysm with extensive involvement of the aorta and even with erosion through the sternum so complete that pulsation is plainly visible on the skin surface and yet the patient will continue to live for a considerable period of time. One such case recently came under my observation where the erosion had existed so that there was a pulsating tumor over the sternum for more than three years. (Fig. 1.)

TREATMENT

This is usually medical and consists of rest and restricted diet and forced antisyphilitic medication. The surgeons have attempted to treat this condition and have been successful in cases of small-

er aneurysms involving the arteries of the extremities. Surgical treatment of large aneurysms of the thoracic portion of the aorta has proved rather unsuccessful. At one time it was thought that by introducing considerable silver wire of small caliber into the sac and charging this wire with a mild electric current coagulation of the blood filling the sac would occur, thus obliterating the cavity. The results were not encouraging enough to justify the general use of the procedure. Hobart A. Hare reported thirty-three cases treated by this method, symptomatic cures being produced.

Allow me to introduce the complete record of a typical case of sacculated syphilitic aneurysm of the ascending portion of the arch of the aorta which will illustrate the principal diagnostic and pathologic points mentioned in the body of the article.

Mr. E. J., married, painter. Referred by Dr. A. D. Dunn, August 7, 1919. Chief complaint—shortness of breath, pain in chest, pain in right arm, weakness and backache.

Clinical History.—Trouble began about six months ago with pain in chest over sternum and transmitted to back on both sides and down the right arm. Pain worse after exertion, relieved by lying down and is not accompanied by fear of impending danger. Great weakness during attacks which come on every three to six hours, lasting from three to five minutes. About two weeks ago patient began to have shortness of breath, palpitation and nonproductive cough.

Physical Findings.—Heart.—Apex beat in the 6th interspace and midclavicular line. Double murmur at aortic area. Presystolic murmur at apex not transmitted. Lung rather coarse, dry rales over both sides of chest, anterior and posterior. A few old snags in the upper jaw. Jugular veins on both sides distended. Dullness in the 1" and 2" interspaces. Pulsation in the 2" right interspace, trachial tug present. Duroziez Carrigan pulse. 10-23-19. Fluid in right chest, resonance and breath sounds markedly diminished in right anterior chest, marked systolic hint over area of diminished breath sounds and increased dullness. Right recurrent laryngeal irritation.

Urinalysis.—Specific gravity, 1016. Granular casts. Blood count, hemoglobin 85 per cent, red blood count, 4,500,000; leukocytes, 8,600; number of cells counted, 100; polynuclear neut. 70; small lymphocytes, 24; large lymphocytes, 6. Sputum, yellow. Wassermann, two-plus, alcoholic, three-plus, cholesterin.

Clinical Diagnosis.—Syphilitic aortitis with sacculated aneurysm of the ascending arch of the aorta. Aortic insufficiency, decompensation of heart. Passive congestion of the liver. Edema of the lower extremities.

X-Ray Findings.—Sacculatation of ascending portion of arch extending to the right and forward, the transverse and descending portions of the arch are not involved. The sac pulsates slightly.

Postmortem Findings.—Superficial glands were palpable in the cervical and inguinal regions. Each pleural cavity contained one liter of clear fluid. The

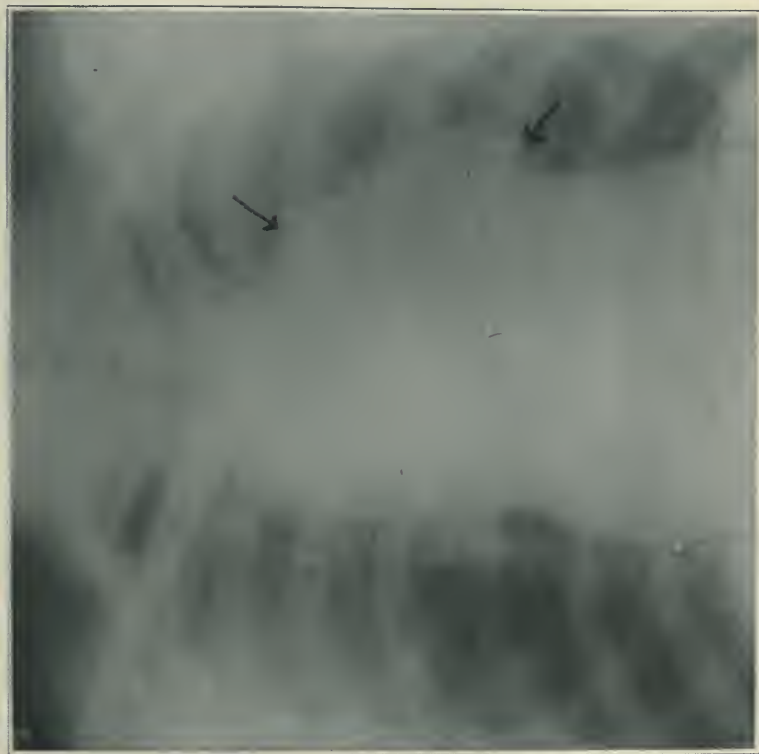


Fig. 7.—Roentgenogram of patient suffering from sacculated aneurysm involving descending portion of arch of aorta. This is an unusual location for the sacculated type due to syphilis.



Fig. 8.—Roentgenogram of patient suffering from lateral curvature of the spine, the concavity to the left. Note apparent enlargement of the heart. Closer observation shows this only apparent as the spine curves around to the right of the heart shadow. Note increased intercostal spaces on the right and decreased intercostal spaces on the left.

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pericardium showed some areas of fibrous thickening and was opaque. The pericardial sac contained about fifty c.c. of yellow fluid. The epicardium showed areas of white fibrous thickening. The heart was enlarged to four times its normal size. The tricuspid ring easily admitted four fingers. The valves were thickened, shrunken, sclerotic and the margins rolled. The heart muscle was pale and flabby. The aortic valves were thickened at the margin, particularly at the copora aurantium and from the margins of the valves up through the arch of the aorta. The aorta was plastered with roughened calcified deposits. In the first portion of the arch of the aorta there was a sacculated dilatation. The orifice measured four cm. in diameter and was sharply marked by rolled edges. The sac measured seven cm. in breadth and three and one-half cm. in depth. The floor was covered with a gray thrombus. The coronary arteries showed marked sclerosis about the orifices with a few plaques through their course. The other parts of the body were negative so far as their connection with the pathology is concerned.

Anatomic Diagnosis.—Serous bilateral pleurisy. Edema and congestion of the lungs. Hypertrophy and dilatation of the heart. Pericarditis, endocarditis, and chronic myocarditis. Chronic aortitis (syphilitic). Sacculated aneurysm of the ascending portion of the arch of the aorta.

ACUTE SYPHILIS OF THE KIDNEY

REPORT OF A CASE

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THAT acute syphilis may affect the kidney has been known for some time and we find as early as 1867¹ the French school reporting cases of this condition. Up to 1898 some 92 cases had been described and they were carefully reviewed by Karvonen. This authority, however, after careful examination refused to accept all these cases and discarded 72 of them. He felt that there was too much chance for error in many of the diagnoses and cases reported. In other words, acute syphilis of the kidney is a rare disease and a physician is probably not justified in making this diagnosis unless exacting conditions are satisfied.

We are aware of the fact that a patient taking hydrargyrum can readily set up a mercury nephritis that may puzzle the physician greatly in its differential diagnosis from a nephritis due to syphilis. Fournier, therefore, set down the following requirements for a definite diagnosis in such a case: (1) Proof of a recent luetic infection. (2) Appearance of a nephritis with a lues. (3) Lack of other sources for the nephritis. (4) Striking characteristics of a nephritis: (a) with a very high albumin content in the urine; (b) with a rapid onset of the kidney disease; (c) with a tendency to early uremia.

Before going further into the discussion of the condition I wish to report a striking example of this interesting and rare condition:

Dan B., age 26, Austrian, white, entered the Cleveland City Hospital the 16th of October, 1919, complaining of a sore on the glans, extreme weakness and loss of 25 pounds in weight. The patient's family history and personal history were negative. He had never had any previous venereal disease. The patient is single. He gave a history that five weeks before, a lesion had started on the glans only two weeks after an exposure. A few days after the exposure he had also developed a purulent urethral discharge. The patient said that about a week before

admittance to the hospital he had noticed an eruption on his body complicated by continual headaches, sore throat and pains all over. He complained especially of extreme weakness and loss of 25 pounds in weight.

Physical examination showed a well-developed and fairly well nourished male.

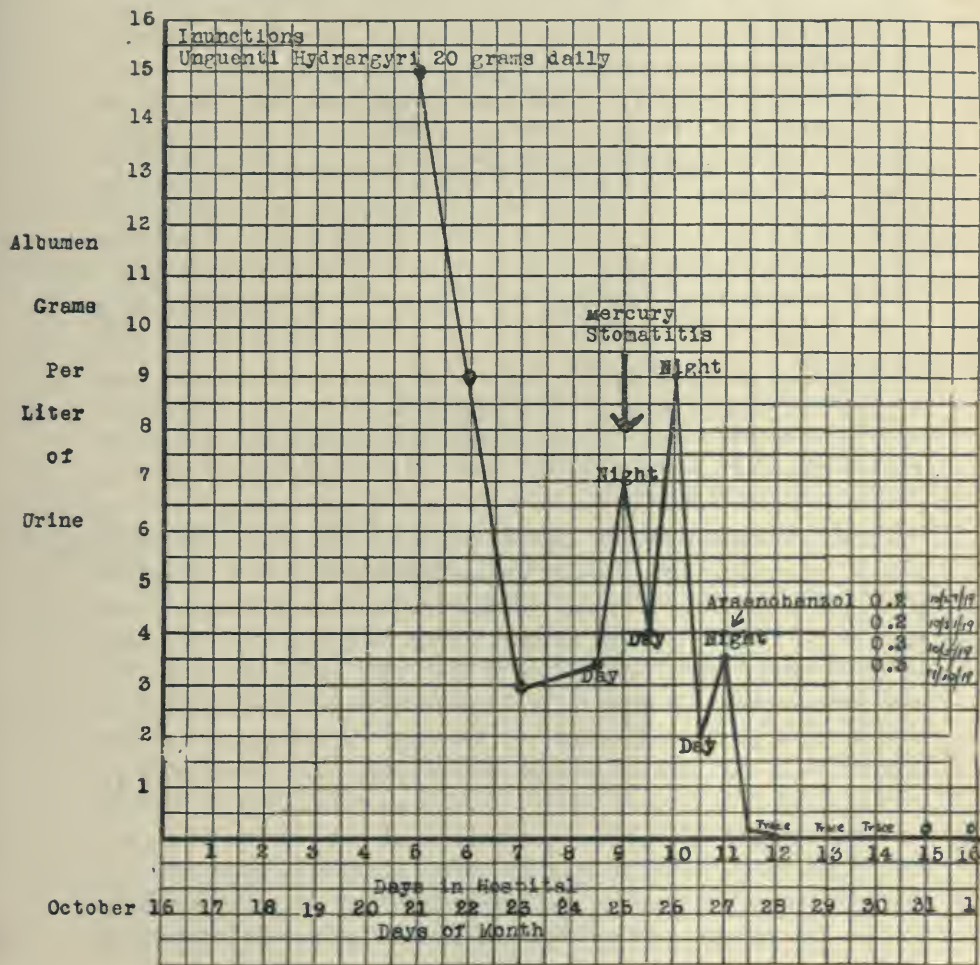


Chart I.

Eyes, ears and nose were negative. There was some injection of the pharynx but no patches were noted on the mucous membranes of the mouth. Patient had general glandular enlargement. Heart, lungs, and abdomen were negative. Examination of the genitalia revealed the shaft to be much swollen with a certain amount of balanitis; several moist papules around the urethral opening and a pro-

fuse discharge. The skin showed a generalized macular eruption of syphilis. Wassermann, four-plus on the blood.

On examination of the urine we were surprised to find that a test tube of urine would boil practically solid with heat and no acetic acid added even after the specimen had been filtered of pus cells. Many granular and hyaline casts were present but by no means enough to explain the albumin which measured with the Esbach albuminometer 15 grams to the liter. Specific gravity 1037.

The renal function showed an excretion of phenolsulphonephthalein 40 per cent at the end of the first hour; 20 per cent end of second hour, total two hours 60 per cent. The blood pressure remained consistently at 110 to 106 systolic and 64 to 70 diastolic. From Chart I it will be noted that though the albumin content dropped on a low protein diet and daily rubs of unguentum hydrargyrum two grams each, yet at the end of seven days it began to rise again on the appearance of a mercury stomatitis. The result following an intravenous injection of arsenobenzol 0.2 gram was striking to say the least. The albumin dropped to an immeasurable quantity and after two more days not even a trace was present.

Examination of the spinal fluid showed a cell count of 19 cells per cubic millimeter with negative globulin and negative Wassermann. The patient had a white count of 8400 with 70 per cent hemoglobin. A differential count of the blood showed 70 per cent polymorphonuclears; 28 per cent small mononuclears and 1 per cent large mononuclears.

Further comment on our case we believe is not necessary. It is one of the rare type which unquestionably satisfies the most stringent demands of Fournier, except for the fact that our patient showed no symptom of an uremia. This fact, however, has been noted by others and Hoffman² says that none of his six cases had this phenomenon. However, he would add the following requirements for a positive diagnosis if possible: (a) Presence of the spirochete in the catheterized urine sediment. (b) Positive Wassermann reaction on the blood. (c) Influence of specific therapy on the albumin in the urine. Our patient, of course, showed a positive Wassermann reaction and the effect of specific therapy. We intended to catheterize him for a search of the *Treponema pallida* but as the patient had an acute gonorrhea this was impossible. Hoffman reports finding spirochetes from a catheterized specimen in one of his cases, nevertheless in my opinion this is not above criticism as it is well known that a patient may have lesions on the inside of the bladder with a secondary eruption. Apparently the most striking symptom in all the reported cases of acute luetic nephritis is the enormous amount of albumin in the urine and there has been found as much as 50 to 100 grams to the liter in one or

two of the cases. Moreover, one never finds enough granular and hyaline casts to account for the albumin.

Many times there is a striking edema in connection with the disease. Dieulafoy³ lays special stress on this point. Parkes-Weber⁴ reports a recent case with a marked chylous ascites and hydrothorax. The patient often complains of weakness and as was noted in our case there is frequently a marked loss in weight with anemia. The sudden onset usually in the first year of the disease is to Dieulafoy and Plieque also a noteworthy characteristic. I quote the above named author as to pathology. "As regards the pathological anatomy of the disorder, this form is a diffuse parenchymatous nephritis. The tubuli contorti are parts most affected and Henle's epithelium undergoes fatty granular degeneration. There is usually no glomerulitis."

Acute syphilitic nephritis is often fatal, this having been true in around 50 per cent of Fournier's cases and is a serious complication. In therapy it is probably well to lessen the protein intake, put the patient on milk diet and first try small doses of soluble mercury injections or of mercury rubs. Chauffard recommends no therapy but milk diet for a few days in order to be sure that it is not due to some other infection. However, in our opinion the warning of Fournier must not be neglected. The patient may very rapidly go into an uremia and we feel that it would be well to start treatment at once in a case of luetic nephritis so unquestionable as our own. Several authors have noted the same experience as ours, i. e., that arsphenamine in small doses seems to be more beneficial and less detrimental than hydrargyrum. In our case the patient became salivated after a week of mercury rubs and his albumin content was steadily rising in the urine. We then tried small doses of arsphenamine with a result that was instantaneous. Stokes⁵ noted the same in one of his cases. It may be well for others to likewise try this drug in such a condition.

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SYPHILIS OF THE BLADDER

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INTRODUCTION

THE literature on syphilis of the bladder is comparatively meager. This is particularly true in regard to British writings, in fact, with the exception of a single case reported by Hinder¹ in the *Australasia Medical Gazette* in 1901, no mention of the condition can be found in British periodicals. In British textbooks the only references to vesical lues are made by Osler and Gibson² in Power and Murphy's *System of Syphilis*, and Marshall³ in his *Syphilology and Venereal Disease*. The former authors devote to this important subject merely the following brief paragraph: "Syphilitic affections of the bladder are extremely rare. Ulceration has been described from breaking down gummata," while Marshall states that the condition is apparently very rare and quotes the cases of Margulies²¹ and Le Fur.⁵⁸

American writers are better represented in the literature of bladder syphilis, and one or more cases have been reported in American periodicals by Morris,⁴ MacGowan,⁵ Lenehan,⁶ Simons,⁷ Schapira,⁸ Pedersen,⁹ Baker,¹⁰ Fowler,¹¹ Denslow,¹² Wallace,¹³ Hays,¹⁴ Cole,¹⁵ and Windell,¹⁶ while in a few American textbooks the condition is discussed more or less fully.

Fuller¹⁷ in Morrow's *System of Genito-Urinary Diseases, Syphilology and Dermatology* admits the possibility of early involvement of the bladder in the syphilitic process and quotes Proksch¹⁸ on the subject of gummatous affections of this organ.

Kelly and Burnam¹⁹ in their *Diseases of the Kidneys, Ureters and Bladder* devote a part of one page to a discussion of the condition, mentioning the cases of Fenwick,²⁰ MacGowan,⁵ and Margulies.²¹

In Chetwood's²² *Practice of Urology* appears the following short account of syphilis of the bladder: "This condition is generally considered to be very rare, which may be due to the fact that

existing specific lesions have gone undetected. Recent cases have been reported of syphilis of the bladder recognized by cystoscopic examination which have occurred in the form of circumscribed areas of inflammatory infiltration involving the interior of the bladder that have been accompanied by a positive blood examination and have disappeared under iodide medication or salvarsan infusion."

In his book on *Syphilis*, Thompson²³ devotes about one page to a discussion of the subject.

Greene and Brooks²⁴ devote a portion of three pages of their *Diseases of the Genito-Urinary Organs and the Kidney* to syphilis of the bladder, quoting the work of Gayet and Favre.²⁵

But by far the most complete dissertation on the subject so far published in the English language is that of Corbus²⁶ in Cabot's *Modern Urology*. This author reviews a considerable portion of the literature and mentions one personal case.

In the French and German literature, both in periodicals and textbooks, we find a considerable number of discussions of syphilis of the bladder, and one or more cases have been reported in the Russian, Italian, Spanish, Portuguese and Swedish literature. To these also, may be added the alleged cases of Morgagni,²⁷ who wrote in Latin.

HISTORICAL AND CRITICAL REVIEW

Nearly all authors who have discussed the history of syphilis of the bladder accredit Morgagni²⁷ in 1741 with being the first to write concerning this type of involvement. However, both Levy-Bing and Duroux²⁸ and Marguliès²¹ quote Proksch¹⁸ as stating that Morgagni was the earliest writer on the subject, yet in the bibliography of each of these articles appears the following: "Cruger,—*De Mictione in somno, syphilide atque ulceribus, Dresdae, 1712,*" but with no mention in the text of this reference. This work of Cruger, or Crausius, as the name is usually spelled, can not be found in the leading medical libraries of this country, neither does it appear in a very extensive bibliography of this writer published by Jourdan²⁹ in 1821. It has, therefore, been impossible to determine whether or not Crausius recognized the condition under discussion.

No mention of syphilis of the bladder can be found in the writings of Astruc,³⁰ who recognized so many other types of visceral

involvement. Neither did the great John Hunter³¹ recognize the condition, but this is not so surprising as he denied the existence of many types of visceral syphilis which others had observed.

Lancereaux³² in 1873 stated that if syphilitic affections of the bladder exist, and that there was every reason to believe that they did, they were as yet but little known.

In 1879 Proksch¹⁸ reviewed the literature and found only six cases, but added no new ones. This was the most complete dissertation of the subject published up to that time.

Noguès,³³ writing in the second edition of Fournier's *Traité de la Syphilis* as late as 1906 critically reviewed some of the cases reported and stated that if syphilis of the bladder really exists it is attested to only by a very small number of cases, and that it certainly is of extreme rarity.

Other more or less complete discussions of the condition, but without the report of new cases, are to be found in the textbooks of Lang,³⁴ Kaposi,³⁵ Neumann,³⁷ Finger,³⁸ Nitze,³⁹ Desnos and Minet,⁴⁰ Joseph,⁴¹ Legueu,⁴² Casper,⁴³ and Fouquet.⁴⁴

An attempt is now made to review all of the cases of syphilis of the bladder to be found in the literature, and these observations are arranged chronologically, each being followed by a critical comment.

OBSERVATION I. MORGAGNI,²⁷ 1741

CASE 1.—(*Libra I, Epis. IV, Art. 19, Tome I, p. 30.*) Man of 60, fat, a heavy eater and drinker, who had been in the hospital once before for apoplexy and once with inflammation of the throat and incontinence of urine. This time he was brought to the hospital partly paralyzed and died ten hours later. At autopsy the coats of the bladder were found thickened and began in some places to be almost ulcerated.

CASE 2.—(*Libra III, Epis. XLII, Art. 2, Tome I, p. 156.*) A knight of 46, who had been infected with lues and gonorrhea had pain in making water and involuntary discharge of urine. At autopsy nothing abnormal was found in the bladder, "except a slight abrasion about the orifices of the ureters. (*praeter levem quandam abrasionem circa ureterum orificia.*)"

CASE 3.—(*Libra III, Epis. XLII, Art. 40, Tome II, p. 176.*) In this case Morgagni dissected the body of an old man who was a foreigner (no history is given) and states that there is no doubt that he was infected with the venereal disease. "The bladder was large, having its walls thickened and purulent. (*vesicam autem magnam, crassis parietibus, purulentam.*)—The glans penis was hollowed out with many deep cicatrices. (*Hujus glans pluribus profundus cicatricibus excavata.*) The epiglottis was not perfectly sound, and the nearest

part of the tongue which was covered with glands, was here and there disfigured with little ulcers. (*epiglottis integerrima non erat, proxima autem linguae pars quae glandulis operata est, hic illic ulcusculis foedabatur.*)''

CASE 4.—(*Libra III, Epis. XLIV, Art. 15, Tome II, p. 199.*) A decrepit old man, who had been severely affected for many years with a lues venerea and a gonorrhea for twelve years, died of these disorders. "The uvula, a part of which was wanting, the upper and most posterior surface of the tongue, and the cartilago epiglottis, which had been formerly connected by ligaments, were so full of cicatrices, that nothing could be more so. (*Uvula, cujus pars deerat, linguae superior postrema superficies, & annexa olim per ligamenta epiglottis cartilago ita erant cica cicatricosae, ut nihil magis.*)—We observed the most evident cicatrices from buboes of the groins. (*manifestissimus a bubonibus inguinum cicatrices adnotavimus.*)—Moreover the bladder, consisting of very thick coats—overflowed with a white and turbid humor. (*Perro vesica ex crassissimis tunicis facta—albo turbidoque humore scatebat.*)''

In Case 1, while the possibility of lues of the bladder must be conceded, the evidence is so very slight that it may be disregarded.

In Case 2, although Morgagni states that the patient had been infected with lues, there is no evidence that such was the case, and certainly we have no reason to consider that the abrasions in the bladder were syphilitic.

Case 3 is probably the most quoted of Morgagni's as syphilis of the bladder, but that it was such is most doubtful.

Although Case 4 was possibly one of syphilis, that the bladder was involved is far from certain, particularly when it is remembered that Morgagni states that the patient had been afflicted with gonorrhea for twelve years.

From the above it will be seen that it is at least extremely doubtful whether Morgagni observed syphilis of the bladder, although his observations are of historical interest.

For nearly a hundred years no mention of syphilis of the bladder was made in the literature, but in 1836 Rattier⁴⁵ reported a case which was later reported by Ricord⁴⁶ and has been considered by most writers on the subject as one of bladder syphilis.

OBSERVATION II. RATTIER,⁴⁵ 1836

The patient was a man of 52, who had suffered from gonorrhea on four different occasions, the dates of which being uncertain. On admission to the hospital he was suffering from an orchitis and hydrocele. The latter was punctured by Ricord, but reappeared in three days when it was again punctured. In a short time the patient left the hospital cured of his orchitis and hydrocele,

but with a persistent urethritis. However, he soon returned with his condition as when first admitted. The hydrocele was again punctured by Ricord, but the gonorrhea continued to progress and death followed. At the autopsy a large ulceration was found which had destroyed three-fourths of the urethra. Several rounded ulcerations of characteristic venereal formation affecting all the coats appeared on the surface of the bladder.

This case can scarcely be considered one of syphilis of the bladder, as there is no evidence to show that the patient was suffering from syphilis, although the possibility must be admitted.

OBSERVATION III. FOLLIN,⁴⁷ 1849

The bladder of a woman, age not mentioned, was presented by Follin before the French Biological Society in 1849 on the inner aspect of which there were a dozen tumors the size of a lentil and raised about a millimeter above the surrounding surface. These tumors bore a marked resemblance to "mucous tubercles" observed on the labia majora. The syphilitic nature of the bladder lesions appeared more probable to Follin inasmuch as the soft palate and palatine vault had been destroyed by syphilis.

This case seems to be one of true syphilis of the bladder and should be accepted as such, although even in this case absolute proof of syphilitic nature of the lesions is lacking.

OBSERVATION IV. RICORD,⁴⁶ 1851

CASE 1.—This case is the same as the one reported by Rattier⁴⁵ in 1836 and while, as stated above, it has been considered by the majority of writers on the subject as one of syphilis of the bladder, the evidence in Ricord's report is no more convincing than that in the report of Rattier.

CASE 2.—Ricord's second case was in a young man of 18, who contracted a chancre of the frenum some days following a suspicious intercourse. The sore spread from place to place, encroaching on the meatus, and in a short time an abundant discharge developed with painful urination. Soon a phimosis formed which was relieved by incision, but the edges of the wound ulcerated, and the ulceration spread to the glans which was almost completely destroyed. For three months the discharge persisted with pain and incontinence of urine, followed by death from marasmus. The autopsy revealed an ulceration of the meatus which had encroached on the urethra, and a second elongated ulceration in the membranous and prostatic portion of the urethra. The neck of the bladder was partly destroyed, while the walls were hypertrophied and the mucous membrane ulcerated and covered by elevated tumors.

While the evidence in this case is only presumptive, it should be accepted as one of syphilis of the bladder.

OBSERVATION V. VIRCHOW,⁴⁸ 1852

In a woman of 84, who had presented symptoms of syphilis for fifteen years and in whom there had been incontinence of urine for the past month there were found at autopsy ulcerations of the bladder and urethra.

While this case was possibly one of syphilis of the bladder the evidence is not sufficient to warrant such a diagnosis.

OBSERVATION VI. VIDAL DE CASSIS,⁴⁹ 1853

A man of 26, who had had a chancre of the sulcus coronis three years previously with very little treatment but with healing of the lesion in three or four months. At the time of entrance into the hospital he presented a urethral discharge, marked abdominal pains, hematuria after micturition and retention of urine. On the fifth day he succumbed to generalized peritonitis. The autopsy revealed a vesico-peritoneal fistula, and on the right side of the mucous membrane of the bladder there was an elevated ulceration about the size of a 20 centime piece with the edges cut into peaks.

As with Ricord's second case the evidence in this case is only presumptive, but it seems sufficient to accept it as one of syphilis of the bladder.

OBSERVATION VII. VIRCHOW,⁵⁰ 1858

A man of 47, who had contracted syphilis twelve years previously, entered the hospital with marked dyspnea and edema of the lower extremities. There was a systolic murmur at the apex and an accentuation of the second pulmonary sound. In spite of treatment the patient died three days later. At the autopsy many of the organs presented marked changes, while the bladder walls were greatly thickened and near the opening of the ureters there was a shining, red swelling of the mucous membrane.

The evidence in this case is entirely too indefinite to include it in the list of cases of syphilis of the bladder.

OBSERVATION VIII. TARNOWSKY,⁵¹ 1872

The case reported by Tarnowsky was in a male child of 4, which had been infected by its foster mother. As a diagnosis of syphilis was not made at first, and treatment for eczema had been instituted, the condition of the child on entrance to the hospital was deplorable. The body was covered with oozing and ecchymotic papules, and in the mouth and throat were many ulcerations and mucous patches separated by deep fissures, while there was great difficulty of respiration and complete anorexia.

After the child had been in the hospital four days it was observed that at

each urination there was extreme agitation and there were apparently severe pains in the genital region. The prepuce was found on examination to be greatly swollen and inflamed, and the urethra was indurated and painful. Upon puncture of the preputial sac a purulent, greenish-yellow fluid escaped. On the twelfth day after entrance into the hospital the patient died, and the autopsy revealed the mucous membrane of the urethra and part of the bladder covered with superficial syphilitic ulcerations. The pharynx and throat were sprinkled with ulcerated papules, and the liver was syphilitic.

This case was undoubtedly one of syphilis of the bladder.

OBSERVATION IX. UVA,⁵² 1882

A man of 30, who had masturbated in childhood and who was later much given to sexual intercourse, contracted gonorrhea at 21, and soon after syphilis. This was followed by "careless" treatment. At the time of entrance into the hospital he complained of headache, local pains, paralysis, and a sense of pain in the abdominal region which was accentuated when urinating. Upon examination it was found that a metallic catheter could not be introduced, but a rubber catheter was inserted without obstruction in the urethra, but as the end of the catheter entered the bladder it was stopped by an impediment which gradually gave way. Urine flowed, but was cloudy and had an ammoniacal odor. The flow was slow though pressure to the hypogastrium was applied, and at the end a black clot was passed which had the odor of feces. Two fingers' breadth above the symphysis pubis, and two fingers' breadth to the left of the median line a tumor was felt the size of a small apple which could also be felt with the finger in the rectum. The urine always had a fecal odor and the patient became weaker and weaker and finally died.

No autopsy report is given and although Uva considered it one of syphilis of the bladder the evidence does not seem sufficient to warrant such a diagnosis.

OBSERVATION X. FIORANO,⁵³ 1887

A young man, age not given, had once had an "ulcer" which was followed by general syphilis, for which he was treated. A few months prior to his examination by Fiorano bloody urine appeared and has continued ever since. Cold, styptics, etc. applied with no avail. Urination was not frequent or painful. The patient was weak and the two epididymes were enlarged and hard, the inguinal glands were enlarged and on the side of the neck there were many copper-colored or coffee-brown papules. A diagnosis of either tuberculosis or syphilis was made, but as no tubercle bacilli could be found, mercurial treatment was instituted. The papules disappeared, the epididymes became normal and the blood in the urine ceased.

This is the first case reported in which the therapeutic test was used and was probably one of syphilis of the bladder.

OBSERVATION XI. NEUMANN,⁵⁴ 1896

A woman of 44, in whom no history of syphilis is given, presented in the bladder numerous whitish round nodules about the size of a millet-seed, some isolated and some in groups.

The amount of data in this case is entirely too meager to justify the diagnosis of syphilis of the bladder.

OBSERVATION XII. MORRIS,⁴ 1897

A woman of 50 with no specific history consulted Morris for cystic hematuria with pain at the end of micturition of one month's duration, which was getting worse. She had lost thirty pounds in weight. The urethra was patulous and in the left upper quadrant of the bladder was a point of special tenderness. The cystoscope revealed clear urine coming from the ureters. No favorable results followed local treatment and the use of ergot, strychnine, etc. About a month later a mass was passed from the bladder which showed small round cells and fibrous growth. A diagnosis of gumma was made and Hardaway's mixture was ordered. The hematuria rapidly subsided and in two months the patient was well.

This was the first case in which the cystoscope was employed, although nothing definite was learned by its use. This was also the first case in which a diagnosis was made by microscopic examination of tissue.

OBSERVATION XIII. GRIWZOW,⁵⁵ 1899

CASE 1.—A woman of 42, who had had syphilis for ten years, at the time of examination presented symptoms of pain and intermittent retention of urine, which had been diagnosed chronic catarrh of the bladder and which had not yielded to irrigations for two and one-half years. On palpation a compact, rounded tumor could be felt below the pelvis which was also palpable through the vagina. At the same time there was pain in the liver region, with palpable hepatic nodes, diarrhea, and vomiting, which caused a diagnosis of hepatic gummata to be made. The use of mercurial treatments for several months caused the liver symptoms to disappear, and also the cure of the vesical condition as well as the disappearance of the subpubic tumor.

CASE 2.—A man of 30 had contracted syphilis six years previously and had complained of pain on micturition for two years which had persisted in spite of local treatment. There was also a perforation of the hard palate. The bladder symptoms disappeared under mercury.

In each of these cases there is a definite history of syphilis, with manifestations other than the bladder symptoms of the disease, and a clearing up of the bladder symptoms under mercury.

OBSERVATION XIV. MATZENAUER,⁵⁶ 1900

A girl of 22, who had contracted syphilis four years previously, was examined with the cystoscope, although no history of bladder disease is given in the report. Many papilloma-like projections resembling villousities were observed covering the neck of the bladder, while the remainder of the bladder wall was normal. A diagnosis of gumma of the bladder was made.

While this case was possibly one of syphilis of the bladder, and was the first one reported in which such a diagnosis was made cystoscopically, the evidence is not sufficient, and, therefore, can not be accepted.

OBSERVATION XV. MACGOWAN,⁵ 1901

A man of 37 contracted a venereal ulcer in 1891, for which he received but little treatment, although no so-called secondaries developed. Six years later he suffered with a severe diarrhea which persisted for several months, and later a circinate, scaly eruption developed on the penis and arms which was diagnosed as ringworm, but failed to yield to the usual treatment for that condition. These lesions, however, cleared up by the use of calomel collodion and intradermic injections of sublimate. Two years following this a proctitis developed and the urine was found to contain pus. Eleven months later he returned complaining of loss of weight, pain in the bladder, frequency of urination and incomplete retention. Examination of the prostate and seminal vesicles revealed the left side of the prostate nodular and pus appeared at the meatus while massaging. At first there were six ounces of residual urine and thirteen days later thirty-four ounces. The cystoscope revealed the right ureter sunken and dilated into a long slit with a large ulcer posterior to the opening. A diagnosis of syphilis was made and mercury rubs instituted. However, a suprapubic cystotomy was performed, the ulcer curetted and a drainage tube inserted. He was then placed on mercury and potassium iodide and in two months the only evidence of the old trouble was a lack of sufficient contractile power in the bladder and occasionally a few flakes in the urine.

This case was undoubtedly one of gummatous ulcer of the bladder and was the first one in this country to be diagnosed cystoscopically.

OBSERVATION XVI. CHRZELITZER,⁵⁷ 1901

A man of 45, who had had gonorrhea at the age of 20, but who gave no history of syphilis, complained of pains in the bladder and retention of urine. He was treated for cystitis for some time with little effect. Later enlargement of the testicles with small tubercles on the surface and psoriatic lesions on the palms of the hands were discovered. A diagnosis of syphilis was made and antiluetic treatment brought about a disappearance of the vesical symptoms.

The clearing up of the bladder symptoms under antiluetic treatment seems sufficient to warrant a diagnosis of syphilis of the bladder.

OBSERVATION XVII. HINDER,¹ 1901

A man of 55 with no history of syphilis, but who presented scars on the legs, nine months previous to examination began to have more frequent urination and at the end of the act a little blood, without apparent cause. About three months later the loss of blood at times was profuse. At the time of examination there was no pain, but there was more or less straining at the end of urination which occurred every two or three hours by day and two or three times at night. The cystoscope revealed a large, irregularly shaped, deep-cut ulcer about one and one-half inches behind the left ureteral orifice from the lower edge of which there was slight oozing of blood. The patient was put to bed and placed on 12 grains of potassium iodide *t.i.d.*, but with no local treatment. Ten days later the cystoscope showed the ulcer shrunken and more shallow. There were two or three other stellate fissured ulcers, bright red in the center and surrounded by a pink blush. The bleeding ceased at the end of the ninth day, and a week later only one small, superficial, postprostatic patch could be discovered. In one month the patient left the hospital well.

In this case the cystoscopic picture and the clearing up of the bladder symptoms under potassium iodide constitute sufficient evidence to warrant a diagnosis of syphilis of the bladder.

OBSERVATION XVIII. LE FUR,⁵⁸ 1902

A man of 32, who had had syphilis eight years previously, had never had gonorrhea, and had received very irregular treatment. Two years prior to examination hematuria appeared and had occurred at irregular intervals since. The hematuria lasted throughout the act of urination, but was not accompanied by pain or other bladder symptoms. A few months prior to examination a more severe hematuria than usual developed which caused retention of urine due to the formation of clots in the bladder. The hemorrhage was stopped by the aspiration of the clots, but undoubtedly had been profuse as the patient's mucous membranes were very pale. The urine was turbid and contained many red blood cells and leucocytes, but no bacteria. The prostate was hard and irregular, and there could be felt a large, hard nodule in the right lobe. Le Fur suspected that the hemorrhage was due to a chronic prostatitis and instituted treatment for that condition which was without beneficial effect. A cystoscopic examination was made which revealed a group of three ulcers in the region of the trigone, one of which was rather deep, which had fissured edges and a gray base. A diagnosis of infection of the bladder from the diseased prostate was made and irrigations with silver nitrate solution begun. As the urine still remained turbid under this treatment, and as syphilitic patches developed in the pharynx, it was decided that syphilis was the cause

of the bladder disease, and antisymphilitic treatment resulted in complete recovery in a short time. The urine became clear and free from blood, the prostate soft with disappearance of the nodules, and the cystoscope revealed white scars in place of the ulcers of the bladder.

The evidence in this case is most conclusive and it undoubtedly was one of syphilis of the bladder.

OBSERVATION XIX. MARGULIÈS,²¹ 1902

CASE 1.—A woman of 41, who gave no history of syphilis, who had borne four children and who gave a history of one seven months abortion, complained of painful and frequent micturition with hematuria. The cystoscope revealed three small pea-sized tumors, just external to the left ureteral opening, which were surrounded by an area of light hyperemia. A diagnosis of carcinoma was made, but as operation was refused, and on account of the history of abortion, she was placed on mercurial treatment tentatively. All symptoms disappeared, and in three months only a faint scar remained at the former site of the tumors.

CASE 2.—A man of 35, who had contracted syphilis six or seven years previously, and who had been treated by mercurial inunctions, complained of most violent and excruciating pains in the bladder with frequent urination. The urine was clear and pale yellow in color and contained few leucocytes, red cells and epithelial cells. Cystoscopy revealed a normal vesical mucous membrane and normal ureteral orifices, except just above the left ureteral opening was found a linear ulceration with a jagged border, a grayish base and surrounded by a deep red circle. Under mercurial inunctions and potassium iodide there was complete healing, with the exception of a small cicatrix.

CASE 3.—A man of 55, a tabetic, who gave no history of syphilis, but who presented a small scar on the dorsum of the penis. He complained of a constant desire to urinate. Hematuria was present, and he also suffered from a nephritis which was manifested by a large quantity of albumin and edema. A diagnosis of syphilitic cystitis was made and mercurial treatment resulted in the disappearance of the bladder symptoms. Cystoscopy after treatment showed many trabeculæ of the bladder wall.

Cases 1 and 2 were undoubtedly syphilis of the bladder, but in Case 3 the bladder symptoms probably were the result of the tabes and were not directly due to the involvement of the bladder in the syphilitic process.

OBSERVATION XX. TOVBIEN,⁵⁹ 1904

A man of 41, who had had syphilis thirteen years previously for which he was treated, and in whom a saddle nose developed three years later, complained of pains and hemorrhage on urination which occurred every five or six minutes. The urine contained a few red cells, many leucocytes and much mucus. There was great infiltration in the external orifice of the urethra and ulceration of

the mucous membrane. A diagnosis of gumma of the neck of the bladder was made as the condition did not clear up under irrigations with bichloride, but was cured by the use of specifics.

This case was possibly one of syphilis of the bladder, but the record is so incomplete that it is impossible to determine with accuracy whether it was or not.

OBSERVATION XXI. GRÄFFE,⁶⁰ 1906

A man of 56, who had contracted gonorrhea and small ulcers of the penis thirty-five years previously, was admitted to the hospital for repeated hemorrhages from the bladder and difficulty of urination. There had been pain in the perineum and limbs' extending sometimes to the glans penis, for some months, and there was a moderate doughy swelling, but no pain, in each testicle. Catheterization was difficult owing to a contracted external urethral orifice, and cystoscopy could not be performed on account of the bladder hemorrhage. The urine was bloody and purulent, but no tubercle bacilli or other bacteria could be demonstrated. There was some general improvement following bladder irrigations with weak silver nitrate solution and the hemorrhage and other symptoms decreased. Cystoscopy, which was now possible, revealed at the summit of the bladder a tumor-like new growth with a defect in the center and papillary proliferation of the edges. A diagnosis of papilloma, or several small papillomata, was made and a supra-pubic cystotomy was performed. At the summit of the bladder there was an ulcer extending into the muscular layer, from the base of which white particles could be removed. The ulcer was cauterized, the bladder sutured with drainage through a catheter, and the wound healed uneventfully. At this time a diagnosis of syphilis, which had been thought of before, was made. This was confirmed by the result of antisyphilitic treatment, the patient being discharged completely cured six weeks after the operation. The excised piece of tissue was found to consist chiefly of necrotic cell masses and bladder epithelium which did not show any tumor degeneration.

The evidence in this case seems sufficient to warrant a diagnosis of syphilis of the bladder.

OBSERVATION XXII. FRANK,⁶¹ 1909

In 1909 Frank exhibited before the Deutsche Urologenkongresses in Berlin seventeen pictures illustrating two cases of syphilis of the bladder, showing the lesions before, during and after treatment, with the statement that full publication of the cases would appear later.

It has been impossible to find this publication of these cases, so they will not be included in the present list of authentic cases of syphilis of the bladder.

OBSERVATION XXIII. FENWICK,²⁰ 1910

According to Casper²⁰ Fenwick reported a case from the postmortem records of the London Hospital for 1879 who was admitted to the hospital for a stab wound and died from the injury. At the autopsy there was found a chancre of the penis, and inguinal and lumbar adenitis. On the mucous membrane of the bladder were elevated spots which resembled condylomata.

As no further mention of this case can be found in the literature, and as the above report seems too meager upon which to base a diagnosis, it will not be included in the present list.

OBSERVATION XXIV. LENEHAN,⁶ 1910

A man of 39, who had contracted syphilis six years previously, had had frequent urination and bloody urine for a little over a month, and had lost twenty-five pounds in weight. The urine showed many red blood corpuscles. At this time the patient was too sensitive for cystoscopy, so irrigations with boric acid and weak solutions of silver nitrate were instituted which improved the symptoms. Soon after this the throat became sore and the history of syphilis was obtained. The cystoscope now revealed the mucosa of the entire bladder mildly inflamed and a nodular mass from the ulcerating surface of which blood was oozing. The tumor was situated at the base of the bladder just anterior to the trigone and was about the size of a chestnut. A diagnosis of gumma of the bladder was made and intramuscular injections of 0.1 gr. of gray oil were begun. On the third day the blood began to disappear from the urine, and in four weeks of mercury and potassium iodide treatment the bladder was normal.

The evidence in this case is very convincing.

OBSERVATION XXV. HABEREEN,⁶² 1911

A woman of 41, who at the age of 14 was said to have had swelling on the tongue which healed slowly, and at the same time pains in the neck and difficulty of swallowing, had since talked with a nasal voice. Two years later she had had sores on the thighs for one year. She was married at the age of 19, had seven living children and no miscarriages. For four years she had urinated every three quarters of an hour during the day and every two hours at night, which had become worse during the past few months. The urine was bloody at the end of micturition and the act was followed by cramps. Part of the uvula was missing, and there was regurgitation of fluid through the nose if the patient was stooping forward. The urine contained red blood corpuscles and pus cells, while the Wassermann was positive. The cystoscope revealed the wall of the bladder smooth and glistening with normal ureteral orifices. The wall of the sphincter was swollen and uneven, while behind it on the left was a round swelling the size of a walnut. Three or four other places were nodular, some of them partly ulcerated and covered with pus. A diagnosis of

gummata was made. Arsphenamine was administered and thirty-five days later the patient was dismissed as cured, the urine being normal and the cystoscope showing a practically normal bladder.

This was the first case to be reported in which the Wassermann was used in the diagnosis, and it was the first case to be reported in which arsphenamine was used in the treatment. Furthermore it is unique in that it was possibly one of congenital syphilis.

OBSERVATION XXVI. PERESCHIWKIN,⁶³ 1911

Pereschiwkin in 1911 reported three cases which he termed "papular exanthem of the vesical mucous coat" (*papulösen Exanthem der Blasenschleimhaut*.)

CASE 1.—A man of 28, who had been ill since the summer of 1909, presented himself with a papular exanthem over the body, papular vegetations on the penis and around the anus, general adenitis and alopecia. He complained of pains in the lower abdomen on urination and frequency of urination. The cystoscope revealed a normal bladder except the base, which was edematous and hyperemic, while around the left ureteral orifice were a few ulcers with raised, infiltrated borders and intensely red base. A diagnosis of syphilis was made and all the bladder trouble disappeared under mercury salicylate, the cystoscopic picture becoming normal.

CASE 2.—A man of 27, who had contracted syphilis in September, 1909, presented himself in November with a roseola, mucous patches in the mouth and anus and a general adenitis, and complained of frequent and painful urination. The urine contained a large number of leucocytes, but was otherwise normal. The cystoscope showed in the region of the vertex four little wounds with infiltrated borders, while the vessels were injected. After seven injections of mercury salicylate urination became less frequent and less painful and the cystoscopic picture became normal.

CASE 3.—A man (age not given) who contracted syphilis in October, presented himself in December with a roseola, papules of the anus and scrotum, mucous patches in the mouth and a general adenitis. He complained of very frequent and painful urination. The urine was cloudy and contained a number of leucocytes, a few red corpuscles and a great deal of bladder epithelium. The cystoscope revealed the vessels of the mucous membrane greatly injected and several ulcers of various size and form, while the ureteral orifices were somewhat edematous. After three injections of mercury the urination became less frequent and painful, while after ten injections urination became normal with no pains and only a few leucocytes in the urine. The cystoscope also revealed a normal mucous membrane with no ulcerations.

These three cases are the first occurring early in the course of the disease to be reported with sufficient data to make a positive diagnosis of syphilis of the bladder.

OBSERVATION XXVII. VON ENGLEMANN,⁶⁴ 1911

CASE 1.—A woman of 47, who gave no history of luetic infection, but who had had three abortions twenty years previously, had suffered from paralysis of both legs for a year and painful urination for a month. Upon examination she was found to have syphilitic myelitis, ulcerated papules of the labia majora, inguinal adenitis, paralysis of the detrusor vesicæ and of the legs. The urine was turbid and contained much pus and many streptococci and Gram negative diplococci. The cystoscope revealed reddening of the bladder, and in the region of the left ureteral opening, and completely surrounding it, a large ulcer covered with encrustation which projected into the bladder. Similar encrusted ulcers were observed in the summit and on the lateral and anterior wall which varied in size up to five centimeters. The encrustations were separated with difficulty with the catheter and hemorrhages resulted. Antisyphilitic treatment and irrigations of the bladder caused slow, but progressive, improvement of all symptoms. The paralysis disappeared, and after two months the bladder mucosa was normal, except for white scars at the sites of some of the ulcerations.

CASE 2.—A woman of 60, who had had syphilis twenty years previously, complained of hemorrhage of the bladder which had lasted six months. The cystoscope revealed above the right ureter a tumor about three centimeters long with ulcerated surface which was covered with a purulent membrane and in places encrustations. The tumor was thought to be a carcinoma, but upon learning the luetic history mercury treatment was ordered, which resulted in rapid healing of the ulcers and disappearance of the tumor in a few weeks.

CASE 3.—A man of 46, who had acquired syphilis fifteen years previously and had been treated with mercury, had suffered from paralysis of the left leg one year previous to the examination, which had disappeared under mercury. At the time of examination he had suffered from hematuria at times for the previous three months. The urine was turbid and at the end of urination there was slight pain. The cystoscope revealed beneath the opening of the right ureter a round, prominent tumor about the size of a hazel nut, the surface of which was partly ulcerated and covered with a purulent membrane and with papillary characteristics in places. A diagnosis of gumma of the bladder was made and antiluetic treatment ordered. After thirty mercurial inunctions the cystoscope showed that the tumor had disappeared leaving a red spot.

All three of these cases undoubtedly were syphilis of the bladder.

OBSERVATION XXVIII. ASCH,⁶⁵ 1911

CASE 1.—A man of 45, who had had syphilis twenty years previously, had for three months prior to examination complained of sudden hematuria which was continuous throughout urination but without other symptoms. The cystoscope revealed papillæ the size of a hazel-nut about 0.5 of a centimeter external to the mouth of the left ureter. Directly above, and partly covered by, the papillæ there was an ulcer one centimeter in diameter with hard, infiltrated edges and grayish-yellow, purulent masses covering the base. Bacterial ex-

amination showed no gonococci or tubercle bacilli. The condition entirely healed under mercury and potassium iodide.

CASE 2.—A woman of 28, who one year and three months previously had had a small ulcer on the left labium which had been cured by local treatment and was not followed by other symptoms of syphilis, at the time of examination presented all the signs of acute cystitis, urinating every half hour during the day and every ten minutes during the night, with persistent and severe stranguary and terminal hematuria. Tuberculosis was excluded and the cystoscope revealed the whole of the bladder mucous membrane much swollen and red, and scattered over it were hard, superficial, round and oval defects in the mucous membrane with small, undermined edges and whitish bases. They resembled mucous patches of the mouth, and, as at this time the patient admitted the sore on the labium and the inguinal glands were enlarged and hard, mercurial inunctions were ordered. During the first week the symptoms seemed worse, but by the end of the second week they began to improve and complete recovery resulted.

CASE 3.—A man of 35, who had had a chancre twenty years previously, which was only superficially treated, had no other symptoms until an ulcer developed on the right thigh five months prior to examination. For three months he had suffered with severe hematuria and for six weeks painful desire to urinate. The urine was turbid and contained many leucocytes and red blood cells. The cystoscope revealed a large gummatous ulcer in the fundus, two or three centimeters in diameter, with greatly infiltrated edges and projecting one centimeter into the bladder and a yellowish base. A diagnosis of syphilis was made and the patient given 0.5 gram of arsphenamine, and after twelve days the gummata of the thigh and bladder had disappeared.

These three cases, also, undoubtedly were syphilis of the bladder.

OBSERVATION XXIX. MIKHAILOFF,⁶⁶ 1911

A woman of 39, who gave no history of syphilis, and who had had a normal parturition thirteen years prior to examination, had complained of pains in the hips for fifteen years and hematuria for five years. The hematuria had grown more frequent and more profuse during the past two years, occurring every two or three weeks and lasting three to four days. The hematuria was unaccompanied by pain and the temperature was normal. The cystoscope revealed the neck of the bladder and trigone very hyperemic. On the lateral and superior walls of the bladder were characteristic rows of vesicles covered by yellowish-gray crusts and each vesicle was surrounded by an area the color of red raspberries which was in deep contrast to the neighboring mucous membrane. Injected vessels were seen here and there, and there were also seen papules similar to those observed on the skin. At first the Wassermann was negative, but a week later was positive, and the symptoms, both local and general, disappeared under mercury and potassium iodide.

There can be no doubt but that this case was one of syphilis of the bladder.

OBSERVATION XXX. NIN POSADAS,⁶⁷ 1911

CASE 1.—A man of 45 had acquired syphilis nineteen years previously, which began with a chancre on the balanopreputial fold and was followed by a roseola, "*corona veneris*," slight alopecia and mucous patches in the left cheek. Fourteen years later he had laryngitis and since then his voice had been somewhat hoarse. Two years prior to examination he had several gummatous ulcerations. He was cured of all these affections by mercurial treatment and occasionally used inunctions and pills of protoiodide. Fourteen months prior to examination, without any apparent cause, he noticed that his urine was tinged with blood. This lasted for a day and a half and recurred every twenty or thirty days, the patient urinating every twenty minutes day and night. The hematuria was accompanied by depression and hot and cold flashes, and at times he passed clots of varying size. At the time of examination the patient was forced to urinate every fifteen minutes, the urination being somewhat difficult and slow. Owing to a stricture of the urethra cystoscopy was impossible. The patient was placed in bed on a milk diet and salol and ergotine prescribed. Under this treatment the hematuria diminished and disappeared completely. At this time dilatation of the urethra was begun and later a cystoscopy attempted which resulted in a severe hematuria lasting several days. A diagnosis of tuberculosis was made but treatment made the patient worse. Antisyphilitic treatment was then resorted to and improvement and apparent cure resulted.

CASE 2.—A man of 25, with no history of syphilitic or other venereal infection, was admitted to the hospital with pain and disturbances of micturition. The urinary symptoms began four months previously by difficulty of urination, a burning in the meatus and urethra after the act and followed by the emission of several drops of blood. Some of the blood was mixed with the urine and sometimes it occurred in the form of small clots. Micturition was frequent during the day and three or four times during the night. The cystoscope revealed an ulcerated surface at the margin of the left ureteral orifice and this was united to another triangular surface apparently covered with pus which extended along the upper wall to two centimeters to the right of the median line. The left margin at this point had a red edge which was not observed elsewhere. The appearance of all this surface resembled mother of pearl. A diagnosis of tuberculous cystitis was made and irrigation of bichloride 1 to 3000 instituted. At first some slight improvement was noted, but as this did not continue, surgical intervention was resorted to. Suprapubic cystostomy was performed and the lesion scraped and cauterized. About six weeks later a diagnosis of syphilis apparently was made, as injections of mercury were begun. This caused considerable improvement both in the urinary symptoms and in the cystoscopic picture and the patient was discharged a month later. However, in about four weeks he returned with the same symptoms as before which again improved under injections of mercury.

The first of Nin Posadas' cases was undoubtedly syphilis of the bladder, but in the second case the evidence is at least extremely doubtful, so it is not accepted in this series.

OBSERVATION XXXI. MUCHARINSKY,⁶⁸ 1912

A man, age not given, who one year previous to examination had had a hard chancre followed by a roseola and some treatment, presented no objective signs of syphilis and no palpable glands. There was no urethral discharge, but there was painful and difficult urination both by day and night. A catheter had been employed for two weeks. The cystoscope revealed a diffuse bluish-red hyperemia of the neck of the bladder and trigone, the middle lobe of the prostate protruded considerably into the bladder which was tense and on the mucous membrane there were flakes of mucus, also an ulcer about the size of a copper coin which had jagged, strongly hyperemic edges was observed on the fundus of the bladder and on the base of the ulcer there was a blood clot. Complete healing followed the use of mercurial injections.

This case is apparently one of syphilis of the bladder and is accepted as such.

OBSERVATION XXXII. PICOT,⁶⁹ 1912

A man of 53, who denied all venereal infection, began to have urinary symptoms eight years previous to examination without apparent cause. Two years later he was operated on for vesical calculi and a year later the cystitis increased, brown masses appeared in the urine and before long most of the urine passed through the rectum. The cystoscope revealed the left ureteral orifice round, large and gaping, while below this the vesical wall was thickened and sclerotic. Large projections were seen and were intersected by longitudinal furrows on which finer ones branched. The right ureteral orifice was elongated transversely, while the surrounding mucous membrane was pale, which was in marked contrast to the deep coloration in the region of the trigone. Both below and above the ureteral orifice and almost touching it were observed small, irregular patches of a clearer red, surrounded by a sort of halo. Above this the vesical wall was covered by numerous ulcerations, more or less deep, of variable size and sometimes confluent. They possessed irregular borders, the bases were red at the periphery and paler in the center, and resembled ulcerous syphilides. The posterior part of the bladder on the right side was observed in a similar condition and in the midst of the projections, in a cavity, a fistula was found. It was irregular, of about 0.25 cm. in diameter and the borders were "cut into peaks." Below this orifice, floating in the liquid, were two blackish bodies (debris of fecal matter). At the summit of the bladder were found small tubercular masses, some confluent, others isolated, and slightly ulcerated at their apices. The Wassermann reaction was positive and there was some improvement under specific therapy.

Even in the absence of a history of venereal infection and although complete improvement did not follow specific therapy, it would seem that this was a case of syphilis of the bladder.

OBSERVATION XXXIII. PICKER,⁷⁰ 1913

A man of 44, who had had syphilis for twenty-five years, complained of itching in the bladder and burning during urination which was worse at the end of the act. The urine was clear and as the adnexa were normal it was thought the pathologic condition was in the bladder. The cystoscope revealed the vault of the bladder smooth and pale yellow, both ureteral folds were clearly defined throughout the entire course, while the openings appeared at the ends of the folds in the form of small, papillæ-like protuberances. The urinary stream from each ureter was strong. Posteriorly the mucous membrane of the trigone was entirely normal and smooth, while on the internal side of the right ureteral fold the cystoscope revealed a swelling about the size of a German kronen piece, which was surrounded by a small livid-red border, which gradually blended into the neighboring mucosa. The surface of the swelling itself appeared yellowish with a tendency to red and was sharply divided by a coarsely lobulated border, which was formed by five segments coming together at an obtuse angle. In the middle of this picture was a depression filled with a white scab about the size of a German heller. Complete cure resulted under the administration of potassium iodide.

This case is apparently one of syphilis of the bladder and is accepted as such.

OBSERVATION XXXIV. LEVY-BING AND DUROEUX,²⁸ 1913

A woman of 28 presented herself for examination with an early generalized infection, probably of about three months' duration. There were erosive papules on the vulva and labia, and intensive roseola on the arms, trunk and thighs, and a bilateral inguinal adenopathy with a positive Wassermann. There were no subjective bladder symptoms and the urine was normal, except for an occasional red blood cell. The cystoscope revealed the right ureteral orifice normal, but around the left ureteral orifice the mucous membrane was edematous and hyperemic and there were also ten small ulcerations, some round and some oval, near here. The bladder condition became absolutely normal under mercury therapy.

The evidence in this case is so striking that there can be no doubt of its authenticity.

OBSERVATION XXXV. SIMONS,⁷ 1913

A man of 24, married, who denied venereal disease and who had three healthy children, had had two years previous to examination hypogastric pains,

dull and dragging, first intermittent and now continuous, which were worse when the bladder was full and were relieved upon urination, which was frequent. One year previous he had had an attack of weakness, loss of appetite, lost fifteen pounds in weight, and was suspected of being tuberculous. The urine was clear, amber, acid and the sediment was normal except for a number of white cells. Cystoscopy revealed in the region behind the trigone several round ulcers with clean-cut edges twice the size of a normal ureteral orifice. On one of these was attached a small blood clot. The left ureteral orifice was not enlarged but covered with a bit of mucus. The right ureteral orifice was slightly enlarged and an ulcerated patch joined it on its lateral aspect. Just mesial to the right ureteral orifice and trigone was a small red spot resembling a tubercle that had not ulcerated. Bladder irrigations with silver nitrate were given and the patient passed from observation for six weeks, when he returned complaining of an exacerbation of the condition, especially of the hypogastric pain. The urine showed red as well as white cells. The cystoscope revealed the trigone and the small part of the trigonal region raw, angry and markedly injected but with no distinct ulceration. Indigocarmine was injected and a dark blue stream appeared from the ureters in twenty minutes. A complement-fixation test (Noguchi) was done and was positive. Deep injections of mercury salicylate were given four or five days apart. After five injections the patient was symptomatically cured of the hypogastric pain and frequent urination. After five more injections a second Noguchi test was negative and the cystoscope revealed a normal bladder.

This case was undoubtedly syphilis of the bladder.

OBSERVATION XXXVI. GAYET AND FAVRE,²⁵ 1914

CASE 1.—A man of 66, who had contracted a chancre at the age of 22 and now had symptoms of tabes, had complained of urinary symptoms for fifteen months previous to the examinations. The symptoms began with a pollakiuria, more frequent at night, which had gradually become worse. Suddenly about six months ago he had experienced a violent pain in the perineum and urethra and at the same time a hematuria developed. The cystoscope revealed the ureteral orifice clearly visible, medium prostatic projection and on its site an ulcer of irregular contour. Two other ulcerating papules, covered by a greenish white exudation, were observed on the upper side of the left ureteral orifice. This suggested syphilis and the Wassermann was positive. Specific treatment was instituted and in a week the hematuria ceased. In ten weeks the ulcerations completely scarred over.

CASE 2.—A woman of 50, who denied venereal history, but who had borne ten children, the first two dying at birth and the third at nine months, had seven years previous to the examination suffered from a perforation of the juncture of the soft and hard palates. The urinary symptoms began suddenly eight days previously with intense hematuria and pain during micturition with pollakiuria. The hematuria continued upon entrance into the hospital and did not

subside under the influence of rest. The Wassermann was positive. Cystoscopy revealed the whole upper part of the bladder sound as far as the ureters. The base of the bladder was raised up and presented an appearance somewhat resembling a large middle lobe of the prostate. Here the mucous membrane was very red and presented several small ulcerations. Under the influence of neoarsphenamine the condition rapidly improved and some time later the patient returned for examination. There had been no hematuria in the meantime and the bladder was now entirely normal, except at the neck there were several ridges and the mucous membrane was somewhat irritated.

CASE 3.—A woman of 35, who had contracted a chancre of the lip eleven years previously, which was followed by mucous patches in the mouth for which she had received some internal medication and mercurial inunctions, had, fifteen days previous to admission to the hospital, developed a sudden hematuria with pollakiuria and pain at the end of urination. The cystoscope revealed the bladder white with normal ureteral orifices. On the other hand the trigone was greatly reddened with a median projection resembling an enlarged middle lobe of the prostate. The periphery of the neck was red and the folds much affected. No ulcerations were observed. Complete recovery followed mercurial inunctions.

All three of the above cases were apparently syphilis of the bladder and are accepted as such.

OBSERVATION XXXVII. SCHAPIRA,⁸ 1915

A man of 46 contracted a chancre seventeen years prior to examination, for which he was treated for two years and discharged as cured. Fifteen years later a rash appeared on the chest and hands which was diagnosed as syphilis. The Wassermann was positive and the patient received five intravenous injections of arsphenamine which caused the rash to disappear and the Wassermann to become negative. At the time of examination the patient had been complaining of pain about the pubes for four or five months with urination every fifteen minutes during the day. About a week prior to examination the patient began to suffer from frequency of urination at night and tenesmus. He had lost thirty pounds and was very anemic. The urine contained pus cells and bladder epithelium. Rectal examination of the prostate and seminal glands was negative. The cystoscope revealed the bladder slightly congested, very trabeculated but with normal ureteral openings. The trigone was very congested and a circular ulcerated patch with infiltrated edges and ragged base about the size of a quarter of a dollar on the left side of the left ureter. Another, similar, but smaller, ulceration was found a little to the right of the first one, and a white, glistening tumor covered by mucous membrane a little way from the left ureteral orifice. Although the Wassermann was negative a diagnosis of syphilis of the bladder was made and a week following an injection of arsphenamine the Wassermann was strongly positive. Under mercury and potassium iodide and local treatment the bladder symptoms disappeared, the cystoscopic picture becoming normal, and the Wassermann negative.

This case is undoubtedly one of syphilis of the bladder and is accepted as such.

OBSERVATION XXXVIII. PEDERSEN,⁹ 1916

CASE 1.—A man of 71, who had contracted syphilis fifty years previously with only "mouth medication" for one month, had suffered so-called "liver attacks" ten years later which were finally cured ten years prior to examination by six weeks of intensive treatment. At this time appeared the first bladder symptoms which consisted of painful and frequent urination and later on hematuria. At the time of examination he had suffered for about five years with sudden profuse hematuria and intermittent retention from time to time. Cystoscopy was difficult but a growth which was thought to be a malignant neoplasm was observed. Cystotomy was protested until antisyphilitic treatment had been tried. This was forced in the hospital but with only partial success. However, at the end of a month cystoscopy was successful and a "fleshy" or compact growth with a few moderate villous formations and an unusual amount of necrosis was observed. Nine months later under more or less continuous antisyphilitic treatment the bladder condition was much improved.

CASE 2.—A man of 34, with a negative syphilitic history presented himself complaining of hematuria which was thought to be due to traumatism from the use of a flexible bougie used for the purpose of dilating urethral stricture. Cystoscopy revealed thickened and diffuse congestion of the mucous membranes and a marked flattened infiltration of the right anterior wall with an open lesion posteriorly. The patient also presented a reddened, semi-fluctuating swelling occupying the right supraspinous fossa which, when cut down upon, was found to be a "full fledged gumma." Under intramuscular injections it healed and within four weeks cystoscopy showed a general improvement of the bladder. The patient disappeared for nine months when he again reported complaining of a recurrent hematuria, when he was again placed upon antisyphilitic treatment the result of which is not recorded as he was still under treatment when the case was reported.

CASE 3.—A woman of 44, who twenty-five years previously had borne a child which presented, soon after birth, an eruption diagnosed as congenital syphilis which was successfully treated. Seven years previous to examination the patient developed frequent and painful urination which was succeeded by hematuria with clots. After being variously treated with little success a diagnosis of syphilis of the bladder was made and the condition improved under intramuscular injections. Five months later, at the time of examination, she was complaining of frequent urination (every fifteen minutes during the day and every half hour at night), the urine being turbid and slightly blood stained. Cystoscopy revealed thickening of the mucous membrane with here and there sharply defined congestion set with ulcers to which mucous-like pellicles were adherent. Near the left ureteral mouth a ridge, its fine edge marked by a linear ulcer, curved upward across the vault of the bladder. Under intramuscular injections she improved rapidly and within ten days she was retaining her urine three hours.

CASE 4.—A man of 62, with a small prostate and with only a dram of clear residual urine, complained of frequent urination and urgency so great that he was liable to incontinence during sleep. Under antisyphilitic treatment alone improvement set in at once and progressed.

CASE 5.—A woman of 30, who had been infected with gonorrhea ten and four years previously had suffered from frequent and painful urination since the first urethritis. She had never been free from the bladder symptoms since. Cystoscopy was negative. Eight months later, however, an ulcer and punctate spots were discovered in the bladder. The Wassermann was found positive and under antisyphilitic treatment there was some amelioration of the symptoms.

Cases 1 and 3 were probably syphilis of the bladder, but the evidence in Cases 2, 4, and 5 seems insufficient upon which to base a diagnosis, Pedersen himself stating that the evidence in Cases 4 and 5 is not conclusive.

OBSERVATION XXXIX. NILSON,⁷¹ 1916

CASE 1.—A man of 44, who denied syphilis but admitted a gonorrheal infection four years previously, and gave a history of ulceration of the nose, which had not healed readily, following intimate contact with a person who had been treated for syphilis. The patient had had recurring hematuria for five years with no objective symptoms. At the time of observation nothing abnormal was found upon physical examination but a slight hardening of one epididymis. The urine was light colored, turbid, alkaline, but without albumin or red cells. Three tests for tubercle bacilli were negative. Cystoscopy revealed numerous ulcerations in the bladder and cicatricial changes which suggested tertiary syphilis. The patient failed to complete the course of treatment advised, and although normal conditions in the bladder were soon restored he succumbed three years later to aneurysm of the aorta.

CASE 2.—A man of 25, who at first gave no history of syphilis was treated by sublimate instillations for ulcerations of the fundus of the bladder which were thought to be tuberculous in nature. As no evidence of tubercle bacilli was found and the patient later admitted a luetic infection, for which he had received the usual mercurial treatment, he was placed upon mercury injections. A partial cure resulted, but the urinary symptoms returned later.

The first of Nilson's cases was probably syphilis of the bladder, but in the second the data are entirely too meager upon which to base such a diagnosis. It is therefore, not accepted in this series.

OBSERVATION XL. GOUVEA,⁷² 1916

CASE 1.—A woman of 50, who gave no history of syphilis, and although married had never had any children, presented the symptoms of a tumor of the

bladder. She was bedridden and urinated every half hour, the urine being mixed with blood. The cystoscope revealed a healthy bladder, slightly hyperemic, except just below the outside of the left ureter there was a large globular tumor highly vascular, but without any ulcerations. The Wassermann test was negative, but the strange appearance of the tumor led to a diagnosis of gumma of the bladder. Specific treatment was begun and the patient gradually improved until three months later the cystoscope showed the bladder to be perfectly sound.

CASE 2.—A man of 34, who had suffered from a slight gonorrhea four months previously, and during treatment a small ulceration on the lip, which quickly healed under neocarsphenamine had complained of a profuse hematuria for several days preceded by severe pain in the left kidney. At the time of examination the urine was normal, but the cystoscope revealed a series of scattered papules around the left ureteral orifice, which was rather congested. All of the bladder symptoms, including the hematuria, yielded to antisyphilitic treatment.

The evidence in both of these cases seems to be sufficient to warrant a diagnosis of syphilis of the bladder.

OBSERVATION XLI. BAKER,¹⁰ 1917

CASE 1.—A woman of 19, who denied all venereal diseases, but who admitted sexual indiscretion, complained of pains in the bladder and frequent and painful urination. There was no hematuria, although the urine was cloudy at times. On examination the patient was found to be well nourished and of good color with negative chest and abdomen and a little tenderness over the bladder. The lymph glands were not enlarged. Urine obtained with a catheter was clear with no pus cells, but contained a few red cells, and squamous epithelium. Cystoscopy was attempted, but owing to the pain was not completed. Later under anesthesia cystoscopy was performed and revealed the vesical mucosa deep-red in color, smooth and glistening, normal blood vessels and normal ureteral orifices. The left antero-lateral portion was covered with a livid mucous membrane, but with no ulcerations. The bladder was treated locally and some days later a soft red spot was noticed on the labium majora and syphilis was suspected. Antisyphilitic treatment was proposed and the bladder symptoms entirely disappeared after several months.

CASE 2.—A woman of 22, with no history of venereal disease, but admitted frequent exposure, had complained of symptoms of severe chronic cystitis but with no hematuria for five years. A diagnosis of syphilis of the bladder was made upon a suggestive syphilitic eruption on the labia, irritable condition of the bladder, deep hyperemia of the vesical mucosa, a strong Wassermann reaction and marked improvement upon treatment.

That both of Baker's cases were syphilis of the bladder seems probable, so they are included in the present list.

OBSERVATION XLII. FOWLER,¹¹ 1917

A boy of 19, with no syphilitic history, had complained of frequent and painful urination and passing of small blood clots for the past three months. Upon examination the patient was found to be healthy looking, chest and abdomen negative, external genitalia normal. The urine was uniformly turbid, giving a slight cloud of albumin. As the inguinal, axillary and epitrochlear glands were enlarged, syphilis was suspected and the Wassermann was found positive. Cystoscopy revealed a marked cystitis, the vesical mucosa being obscured, and a small ulcer by the side of the right ureter, which was bleeding. The appearance of the ulcer was suggestive of tuberculosis, but all tests were negative. Arsphenamine was administered as a therapeutic test and the following day the patient noted a definite decrease in urination and improvement was continuous and rapid. Under further arsphenamine and mercury three months later the patient was normal.

Although there was no syphilitic history in this case the improvement of the bladder condition was so marked under antisymphilitic treatment it was undoubtedly one of syphilis of the bladder.

OBSERVATION XLIII. CORBUS,²⁶ 1918

A young man, age not given, who was suffering from so-called secondary syphilis with a diffuse macular eruption, gave no urinary symptoms. However, cystoscopy revealed the mucous membrane diffusely hyperemic. The vessels were injected and numerous islands of mucus were adherent throughout.

Although this case was probably one of asymptomatic syphilis of the bladder the data concerning it are too meager to warrant its inclusion in the present series.

OBSERVATION XLIV. DENSLOW,¹² 1918

A man of 23, who had a history of "chancreoid" two years previously, who had had two negative Wassermann reactions and gonorrhea for one year, complained of frequent urination (every half hour) followed by mucus discharge at the end of the act. Cystoscopy revealed some papillomatous masses at the vesical margin, some protruding into the prostatic urethra. The bladder mucosa was intensely congested and bled easily. Suprapubic cystotomy was performed and the mucosa was found studded, especially at the base, with condyloma-like nodules, deeply involving the bladder wall. There were forty or more of such nodules, some being as much as one-half an inch long. The bladder was everted, with a sharp curette and as many of the nodules destroyed as possible. Sections of the latter were made and diagnosed as syphilitic condyloma and the Wassermann was then found strongly positive. Under mixed treatment improvement was rapid and in three months perfectly normal conditions obtained.

This case was undoubtedly syphilis of the bladder and was the first one to be recorded in which the diagnosis was made microscopically from sections of the lesion removed at operation.

OBSERVATION XLV. WALLACE,¹³ 1918

CASE 1.—A man of 27, for whom no syphilitic history is recorded, and who was the father of two healthy children, had complained of severe pain over the kidney and bladder three years previously. These attacks lasted off and on for six months, during which time he lost weight. He received some treatment which improved his condition but did not cure it. At the time of examination there was straining and tenesmus, frequent, painful and bloody urination with passing of lumps of mucus. Cystoscopy, under anesthesia revealed the prostate enlarged and a villous growth on the right side near the internal sphincter and another one near the right ureteral orifice. Antisyphilitic treatment was administered and the growth completely disappeared.

CASE 2.—A woman of 43, who had had one miscarriage, one child who died at birth and one healthy child of 16 years, with no venereal history, complained of painful, frequent and bloody urination. The urine showed a small amount of albumin and a number of granular casts. Cystoscopy revealed both ureteral orifices thickened, a number of papules and ulcers on the internal sphincter and several in the urethra. The trigone was thickened, showing small nodes and three distinct ulcers irregular in outline. The condition resembled tuberculosis but the Wassermann was positive and the lesions cleared up under specific treatment.

CASE 3.—A man, whose age is not recorded and who denied venereal diseases, was suffering with terminal hematuria. Upon examination, his physical condition was below normal. He was nervous and apprehensive. The cystoscope revealed an ulcerated and nodular trigonitis, thickened and reddened condition of the bladder, also a distinct ulcer and a few small nodes at the internal sphincter. The Wassermann was positive and the condition cleared up under specific treatment. A later anamnesis developed the fact that the patient's father had contracted syphilis twenty-eight or thirty years ago and Wallace considered this to be a case of congenital syphilis.

CASE 4.—A woman of 30, with a negative venereal history, who had been in poor health for eleven years, during which time she had been operated upon, presumably for kidney disease, had also complained of bladder symptoms more or less during that time. At the time of examination the patient showed tenderness over the bladder. The cystoscope revealed a highly inflamed mucosa, two ulcers at the right of the ureteral orifice, four ulcers on the trigone and the left ureteral orifice thickened with several small ulcers. The internal sphincter contained papules and four or five ulcers which bled. The Wassermann was positive and under antisyphilitic treatment the patient became apparently well.

CASE 5.—A woman, age 28, married, with one child of 5 years, with no venereal history was referred to Wallace for cystitis. Cystoscopy revealed

papules and ulcers on the trigone, a group of small ulcers above the right ureteral orifice and the neck of the bladder was inflamed with a few ulcers and small papules. Attempted fulguration was without success, while the bladder washings did not give relief. At this time the Wassermann was found positive. The local treatment was discontinued and the condition healed under antisyphilitic therapy.

CASE 6.—A man of 40, with no venereal history, who had had a suprapubic cystotomy for a growth of the bladder three years previously, had suffered from frequent and painful urination for three months. The cystoscope revealed a reddened bladder, ulceration over the base and trigonal regions, with a white deposit covering same. The Wassermann was positive and two injections of arsphenamine and other antisyphilitic treatment caused great improvement.

CASE 7.—A man of 29, with no children, who had had gonorrhea twelve years previously, but with no other venereal history, was operated upon two years previously for stone in the bladder. At this time no stone was found but a tumor (papilloma) was removed. Cystoscopy revealed ulceration and a villous growth on the neck of the bladder extending down on the trigone. The Wassermann was positive. The growth and bladder cleared under intensive treatment.

CASE 8.—A man of 29, who had had gonorrhea fourteen years previously and a second attack recently, complained of difficult and frequent urination, much straining and some pain over the bladder when full. Examination revealed a large, soft, tender prostate and stricture of the membranous urethra. The stricture was treated for two weeks when cystoscopy was performed, which showed reddened and thickened bladder walls and a distinct gumma the size of a dime near the left ureteral orifice. The Wassermann was positive. The result of the treatment in this case is not recorded.

CASE 9.—A man, age not given, who had at some earlier date, which is not recorded, been operated upon for a growth in the bladder. At the time of examination he was suffering from a recurrence of his old trouble, such as straining and frequency of urination. His history was negative but the Wassermann was positive. The bladder condition, including the disappearance of the growth, cleared up under antisyphilitic treatment and bladder washes.

Wallace has reported more cases of syphilis of the bladder than any other investigator and in all his cases, with the exception of the last one, the evidence seems sufficient to justify a diagnosis of lues of this viscus.

OBSERVATION XLVI. HAYS,¹⁴ 1918

CASE 1.—A woman of 69, for whom no syphilitic history is recorded, had had two hemorrhages from the bladder and a large ulcer at the top of the bladder, responded to antisyphilitic treatment and one year later was in good health.

CASE 2.—A man of 26, with a history of gonorrhea four years previously complained of inability to retain urine. The bladder gave an appearance of chronic inflammation. The Wassermann was positive and treatment gave prompt relief.

CASE 3.—A woman of 46, for whom no venereal history is recorded, complained of painful and bloody urination. The bladder was slightly ulcerated and a small ulcer was present on the trigone. From the appearance of the bladder a diagnosis of tuberculosis was made, but tubercle bacilli could not be found. The Wassermann was positive and one dose of arsphenamine relieved the painful urination. The case was still under observation when recorded.

In none of these cases is the evidence sufficient to warrant a diagnosis of syphilis of the bladder.

OBSERVATION XLVII. COLE,¹⁵ 1918

A woman of 34, who had had syphilis twelve years previously for which she was treated and had suffered no symptoms of lues since. She had also had gonorrhea twice, ten and eight years prior to examination. The bladder trouble started six years previously with pain on urination and frequency; while two years later a partial acute retention with gross hematuria occurred. At the time of examination there were at times pain in the bladder region with burning on urination and every four or five weeks she suffered tenesmus with hematuria. The Wassermann was double-plus. The urine was acid, contained albumin and many pus cells. Under bladder irrigation and autogenous vaccine there was slight improvement. Three months later the cystoscope revealed a severe trigonitis with edema and a large crescentic ulcer with a necrotic base and covered with pus near the right ureteral opening and another ulcer with indurated edges near the left ureteral opening. There was decided improvement of the bladder symptoms under arsphenamine and mercury. Three months later cystoscopy revealed only a white scar at the site of the large ulcer and no evidence of the smaller. For three years after there had been no return of the bladder symptoms.

This case is apparently one of syphilis of the bladder and is accepted as such.

OBSERVATION XLVIII. HESSE,⁷³ 1918

A woman of 24, who denied venereal disease, but who gave a tuberculous family history, complained of painful urination and gradually became aggravated up to severe and frequent urinary tenesmus. The urine contained a considerable amount of pus and at times there were blood cells, but no tubercle bacilli. The cystoscope revealed peculiar, reddish-brown, circular papules in the fungus of the bladder which were suggestive of syphilis. The diagnosis confirmed by a careful anamnesis, the positive outcome of the Wassermann reaction and the recovery under antisyphilitic treatment.

This case was apparently one of syphilis of the bladder and is accepted as such.

OBSERVATION XLIX. WINDELL,¹⁶ 1919

CASE 1.—A man of 37, with no venereal history, but who developed several indurated areas on the penis two weeks following a circumcision by a general practitioner. About one week prior to examination the patient complained of bladder distress with frequent urination. The urine was cloudy, contained albumin, a few pus cells and epithelium. The cystoscope revealed a trabeculated bladder, a red and rough trigone and healed areas interspersed among large inflamed surfaces. Tubercle bacilli were not present and a von Pirquet test was negative. Local treatment was of little avail and six months after his first visit a diagnosis of syphilis was made and the Wassermann reaction was positive. Treatment for syphilis was instituted but arsphenamine withheld on account of albumin in the urine, until six months later. The results of the treatment are not recorded.

CASE 2.—A man of 58, with no history of syphilis, but giving a history of having had gonorrhea when a young man, had complained of "bladder distress" for a long time. The urine was clear, contained few pus cells but no albumin. The Wassermann test was strongly positive and the cystoscope revealed a trabeculated bladder, scars of healed ulcers, and a slight median bar enlargement. Under active anti-luetic treatment most of his symptoms were relieved.

While the possibility of syphilis of the bladder in both of these cases must be admitted, the evidence as set forth does not seem sufficient to warrant such a diagnosis.

OBSERVATION L. THE AUTHOR'S CASE

A man of 25, who had developed an ulcerated papule of the glans penis three months previously and two weeks following a suspicious intercourse, was seen four days after a typical roseola which was distributed over the trunk, legs and arms, had appeared. He had received no treatment but local cauterization of the chancre. At the time of examination, in addition to the roseola, there was a generalized superficial adenitis and several ulcerating syphilomycodermata on the pharynx and the inner aspects of the cheeks were observed. The spleen was palpable two fingerbreadths below the costal margin. The patient looked ill and his temperature was 101° F. He complained of frequent and bloody urination with slight pain which had begun two days previously. The Wassermann was strongly positive and the urine showed many red blood cells, leucocytes and some bladder epithelium. Cystoscopy under local anesthetic revealed the mucous membrane of the bladder congested and hyperemic, particularly in the region of the trigone, while in the region of each ureteral orifice were a number of ulcerating papules 2 to 3 mm. in diameter with



Syphilis of the Bladder. (Author's Case.)

slightly elevated borders, which appeared like the ordinary ulcerating papular syphilomycoderm or mucous patch of the mouth. At this time the urine was examined by the dark field for *Spirochete pallida*, but none was found. The patient was given 0.3 gram of arsphenamine intravenously and 1 grain of mercury salicylate intramuscularly. In twenty-four hours the hematuria had ceased and the frequency of urination had decreased, while in four weeks, following four injections each of arsphenamine and mercury salicylate all symptoms and outward manifestations had disappeared and the cystoscope revealed a normal bladder.

OBSERVATION LI. WRIGHT,⁷⁴ 1919

A woman, 33, in whom no history of syphilis is recorded, consulted Wright for frequency of urination, with pain. She had undergone four abdominal operations for pelvic pain, the last operation being a hysterectomy. She was treated in the hospital for twelve days by irrigations, without improvement. Cystoscopy revealed a circular lesion about one-half inch in diameter, described by Wright as looking as though some one had run a curette around it and made a blood clot. A diagnosis of superficial gumma was made, and under antiluetic treatment in thirty days she left the hospital, apparently in normal health.

This case was possibly one of syphilis of the bladder, although the data is rather meagre upon which to base such a diagnosis.

OBSERVATION LII. PEUGNIEZ,⁷⁵ 1919

A man of 69, who denied an initial lesion, but who, at fifteen years, had suffered from a psoriasis of the nose, which had yielded to specific therapy. Five years prior to examination he had had a tumor of the stomach and two attacks of jaundice. Three months ago he had complained of sharp pains and urination every hour. There were also traces of fecal matter in the urine. Cystoscopy revealed a perforation behind the trigone and a little to the right of the midline. The remainder of the mucous membrane was red and vascular. The rectoscope revealed a similar perforation. Under antiluetic treatment the urinary symptoms entirely cleared up and the cystoscope revealed cicatrization of the lesion.

There seems to be no doubt but that the above case was one of syphilis of the bladder, with perforation into the rectum.

DISCUSSION

INCIDENCE

Syphilis of the bladder has been considered by most medical men as a rare condition, and certainly, if the literature on the subject is to be considered as an indication of its frequency, such an opinion is justifiable.

Only 84 cases, including the present one, purporting to be syphilis of the bladder have been found in a most exhaustive study of the literature, and for various reasons stated above in these 84 cases the evidence in 26 is not considered sufficient to justify the diagnosis of vesical lues. This leaves but 58 undoubted cases. However, it is not believed that this represents the true incidence of syphilis of the bladder, and I feel very sure that if the condition were more frequently looked for it would be more frequently found. In fact, it seems very reasonable to expect that the vesical mucosa very often, if not always, at some time shares in the early cutaneous and mucous membrane involvement, although certainly not always producing symptoms. I venture the opinion that if the bladder mucosa of every case of syphilis seen in the exanthem stage were examined cystoscopically, in a large percentage involvement of this viscus would be observed. However, the present paper has to deal more particularly with syphilis of the bladder which produces symptoms, and it is thought that if the possibility of lues were more frequently kept in mind by the urologist when treating some of the obstinate cystitides the *Spirocheta pallidum* would more often be recognized as the etiologic factor.

ETIOLOGY

Stage of the Disease.—As just stated it is thought that the bladder mucosa is very frequently the seat of the syphilitic process during the early course of the disease when the skin and other mucous membranes are involved. Of the 58 cases of syphilis of the bladder accepted as authentic, only 7 were recorded as occurring during the first year of the disease, and of these, 1 case (Ricord's Observation IV) was undoubtedly a case of so-called malignant syphilis. In the other 51 cases the length of time following the original infection is recorded in 26 and the bladder involvement occurred from 1 year and 3 months to 50 years after the chancre, the average time being 15 years, although in 9 of these cases it occurred before the tenth year. In 4 cases the stage of the syphilitic infection is not stated by the authors, but from the clinical findings 2 of these cases (Tarnowski, Observation VIII and Pereschiwhin, Observation XXVI, Case 1) must have occurred early in the course of the disease, and the other two (Follin, Observation III and Fiorano,

Observation X) must have occurred late in the course of the disease.

No history of syphilitic infection was obtained in the remaining cases. Of these, 2 (Habereen, Observation XXV and Wallace, Observation XLV, Case 3) were possibly congenital, while the others were undoubtedly of late occurrence. Of these, 4 (Chrzelitzer, Observation XVI, Nilson, Observation XXXVII, Case 1, and Wallace, Observation XLIII, Cases 7 and 8) gave a history of gonorrheal infection, while in 4 more cases occurring in women (Margoulies, Observation XIX, Case 1, von Englemann, Observation XXVII, Case 1, Gayet and Favre, Observation XXXVI, Case 2, and Wallace, Observation XLIII, Case 2) there was obtained a history of abortion or the death of children at birth. In Pedersen's third case (Observation XXXVIII) there was a history of bearing a child diagnosed as syphilitic 25 years previously.

Age.—The ages of the individuals were recorded in all but 5 cases and varied from 4 years (Tarnowski, Observation VIII) to 71 years (Pedersen, Observation XXXVIII, Case 1) and by decades occurred as follows:

1st	1 case
2nd	3 cases
3rd	15 cases
4th	11 cases
5th	14 cases
6th	6 cases
7th	2 cases
8th	1 case

It will be seen that 40 to 75 per cent of the cases in which the age is recorded occurred during the three decades from 20 to 50. And this is to be expected when it is remembered that the average time following the infection at which the involvement of the bladder occurred was fifteen years.

Sex.—The sex is recorded in all of the accepted cases and the condition is found to have occurred 37 times in males and 21 in females or nearly twice as often in the former as in the latter.

Extragenital infection is definitely recorded only once (Gayet and Favre, Observation XXXVI, Case 3), although in Gouvea's second case (Observation XXXVIII) the infection was possibly extra-

genital and in Tarnowsky's case (Observation VIII) it was probably so.

PATHOLOGY

The pathology of syphilis of the bladder has been studied post-mortem, through suprapubic cystotomy and by means of the cystoscope, so that a fairly comprehensive knowledge of the various changes has been obtained.

In the early course of the disease, in which the condition has been studied only by means of the cystoscope, there is more or less congestion of the bladder mucosa which may be likened to the diffuse eruption sometimes seen in the mouth and on the pharynx. Or there may be a distinct papular eruption, either with or without erosion or ulceration. However, the ulcerating papular syphilomycoderm seems to be the most frequent variety of lesion. These papules vary in size from one millimeter to one centimeter in diameter and, as a rule, are more or less elevated above the surrounding mucosa.

The most frequent site of these lesions is around the ureteral orifices, usually around only one, but other portions of the bladder wall may be attacked.

In the later stages of the disease the most frequent type of lesion is the ulcerating gumma. This may be either single or multiple, sometimes, as in Picot's case, (Observation XXXII), almost the entire bladder mucosa being covered with ulcers. These ulcers are round, oval or irregular, and vary from one or two millimeters to several centimeters in size. They are usually of a grayish-yellow color with infiltrated edges and are sometimes covered by crustations. In some cases definite bleeding from the ulcers has been observed through the cystoscope and sometimes a blood clot can be seen attached to the ulcer. The most frequent site of these lesions is around the ureteral orifices, although any portion of the bladder wall may be attacked.

In nearly all cases the mucosa has been more or less hyperemic and inflamed in other places than the location of the ulcers. In two cases, (Vidal de Cassis, Observation VI and Picot, Observation XXXII) there was perforation and the formation of a vesicoperitoneal fistula in the first and a vesicorectal fistula in the second. Sometimes there is only tumefaction without ulceration, the tumors

varying in size from a small hazel-nut to a walnut or larger. In some cases in women tumefaction occurs in the base of the bladder which resembles an enlarged middle lobe of the prostate in men.

Papillomatous tumors have been observed, and even operated upon, as in Denslow's case, (Observation XLII) upon the assumption that they were benign papillomata.

In one case (Mikhailoff, Observation XXIX) vesicles were seen which were covered by yellowish gray crusts.

Occasionally healing of the ulcers has taken place and cicatrices are observed.

Four cases (Follin, Observation III, Ricord, Observation IV, Case 2, Vidal de Cassis, Observation VI, and Tarnowsky, Observation VIII) have been examined at autopsy and three cases (MacGowan, Observation XV, Graffe, Observation XXI and Denslow, Observation XLII) have been studied microscopically, which was also done in Morris' case, (Observation XII). In this case the examination was made of a mass which was passed from the bladder and showed small round cells and fibrous growth. In Gräffe's case the excised piece of tissue was found to consist chiefly of necrotic cell masses and bladder epithelium. The microscopic picture in Denslow's case is not recorded, the author being content with the statement that the sections were diagnosed syphilitic condyloma.

While, as will be seen from the above, the microscopic picture of the lesions of syphilis of the bladder has not been studied very thoroughly, there is no doubt that it is the same as found in similar lesions elsewhere, and, briefly, consists of an infiltration of lymphocytes and plasma cells, proliferation of the fixed cells, and more or less endarteritis.

CLINICAL HISTORY

EARLY INVOLVEMENT

Bladder Symptoms.—In vesical lues, occurring early in the course of the disease, there usually will be symptoms depending upon the nature of the lesions, although in one of the recorded cases (Levy-Bing and Duroeux, Observation XXXIV) no symptoms referable to the bladder were observed. In most of the other cases frequent and painful urination were recorded. In two cases (Gouvea, Observation XL, Case 2 and Thompson, Observation L) there was hematuria which in Gouvea's case was the only symptom.

Urinary Findings.—The urine of early bladder syphilis usually shows red blood cells, but as a rule these are not numerous. Leucocytes and bladder epithelium are also observed.

Other Symptoms.—In all but two of the cases of early involvement of the bladder there have been other symptoms of early syphilis, such as generalized adenopathy, roseola, papular syphiloderma, syphilomycodermata, alopecia, etc.

Wassermann Reaction.—In only two of the early cases of this study (Levy-Bing and Duroeux, Observation XXXIV, and Thompson, Observation L) is the Wassermann recorded, and it was found positive in each case. However, it is reasonable to expect it to be positive in practically 100 per cent of such cases.

LATE INVOLVEMENT

Bladder Symptoms.—The most frequent symptom of late bladder syphilis is hematuria and was observed in 30 of the 51 accepted cases. It may be only slight in amount or it may be profuse; may be continuous throughout the act of urination, or be observed only at the end of the act. Quite frequently hematuria is the only symptom, and is the one which brings the patient to the physician. Sometimes the blood in the urine is passed in the form of clots, although, as a rule, it is mixed with this excretion. If the hemorrhage is marked there is more or less anemia.

The next most frequent symptom of late vesical lues is pollakiuria and was observed in 29 of the 51 late cases which are accepted in this study. This symptom may be so marked as to occur as often as every 15 minutes, but as a rule it is not so frequent.

Pain on urination, sometimes only at the end of the urination, was recorded in 24 cases, and in some cases tenesmus was most severe.

In 9 cases pains in the bladder were observed and these were frequently of a most excruciating character. Pains in the perineum and limbs and extending to the glans penis were also observed.

Retention of urine was recorded in 5 cases, and sometimes it is due to the formation of blood clots.

If perforation should occur and a vesicorectal fistula be formed, as in Picot's case, (Observation XXXII), urine would pass through the rectum and feces would be found in the urine.

Urinary Findings.—The urine in late bladder syphilis as a rule contains red blood cells and very frequently more or less pus. Blad-

der epithelial cells are also more or less numerous. However, the urine may be entirely normal.

Other Symptoms.—In only 6 of the accepted cases of vesical lues occurring late in the course of the disease were other symptoms or clinical findings of syphilis recorded. These consisted of inguinal adenitis, papules on the neck, hepatic gummata, perforation of the hard palate, psoriatic lesions on the palms and soles, part of uvula missing and ulcerated papules of labia majora.

In 6 cases loss of weight is recorded.

Wassermann Reaction.—The result of the Wassermann is recorded in 17 of the cases of late bladder syphilis and was positive in all but one, (Gouvea, Observation XL) and Schapira, (Observation XXXVII) it was negative at first, but a week later it was positive.

DIAGNOSIS

As stated above Morris³ in 1897 was the first to employ the cystoscope in a case of syphilis of the bladder, although nothing concerning the true nature of the pathology was learned by its use. It has also been pointed out that Matzenauer⁵⁶ in 1900 was the first to make a *diagnosis* of syphilis of the bladder with the cystoscope, but his case is not accepted in the present study. It is, therefore, to MacGowan⁴ that the honor belongs of first diagnosing an authentic case of vesical lues by cystoscopy.

However, it will be seen from the above review of the pathology and symptomatology of syphilis of the bladder that there is nothing characteristic, either in the cystoscopic picture or the bladder symptoms. The diagnosis, therefore, must rest upon the history, the presence or absence of other manifestations of syphilis, including the Wassermann, or upon the result of specific therapy.

The early involvement of the bladder in the syphilitic process, when there is nothing but congestion and hyperemia, may resemble simple hyperemia and can only be differentiated by employing the general diagnostic measures just enumerated.

The early ulcerating papules must be differentiated from tuberculous ulcers. The finding of tubercle bacilli in the urine would be strong presumptive evidence of the tuberculous nature of the lesion, while the finding of the *Spirochete pallida* would point to syphilis, although such a finding has not been reported.

The vegetating lesions such as seen in Denslow's case (Observa-

tion XLIV) resemble ordinary papillomata and must be differentiated from these lesions. Therefore, all papillomata of the bladder should cause suspicion of syphilis and a Wassermann should be performed. Also, it would be an easy matter to remove a small portion of such growth through an operating cystoscope for microscopic examination.

Gummata of the bladder, both ulcerating and nonulcerating, may be mistaken for carcinoma. In carcinoma there is usually more hemorrhage than in gummata, but it must be remembered that hemorrhage may be profuse in the latter condition. If a positive diagnosis can not be reached by the general methods, that is, from the history, presence or absence of other manifestations of syphilis and the Wassermann, a portion of the growth removed through the cystoscope and examined microscopically would be conclusive.

Gummatous ulcers may also be mistaken for tuberculous ulcers and the same points are to be considered in the diagnosis as have been enumerated in differentiating tuberculous ulcers and ulcerating papules.

Finally in the diagnosis of bladder syphilis it must be emphasized that all cases of hematuria and pollakiuria should be looked upon with suspicion until other etiology than syphilis be proved, and if necessary the therapeutic test be applied.

PROGNOSIS

The prognosis of syphilis of the bladder in the main may be said to be good. However, of the 58 cases which have been accepted in this study four died. In Follin's case (Observation III) no record is made of the cause of death. Death was undoubtedly due to the malignancy of the syphilitic infection in Ricord's and Tarnowsky's cases, (Observations IV and VIII), while in the case of Vidal de Cassis (Observation VI) the cause of death was peritonitis following perforation and the formation of a vesico-peritoneal fistula.

In Picot's case (Observation XXXII) there was a vesico-rectal fistula and "some improvement under specific therapy" is recorded, while in Baker's second case (Observation XLI) there was "marked improvement." In all of the other cases complete cure followed the use of specific remedies.

PROPHYLAXIS

That vesical syphilis can be prevented in practically all cases of luetic infection is undoubted if the nature of the disease be recognized before it has become generalized and proper therapy be instituted. This statement is made merely for the purpose of emphasizing the importance of dark-field examination for the *Spirochete pallida* of all genital and other suspicious sores.

TREATMENT

The treatment of syphilis of the bladder is the treatment of syphilis, and the more vigorous and intensive the therapeutic measures are carried out the earlier will be the recovery. Arspenamine intravenously should be administered at weekly intervals, and mercury intramuscularly, preferably a soluble salt, or by inunction, is to be pushed to the point of tolerance, while in some of the later cases potassium iodide by mouth or sodium iodide intravenously should be of benefit. Local treatment is of little or no benefit.

SUMMARY AND CONCLUSIONS

1. Only 84 cases purporting to be syphilis of the bladder have been recorded in the literature, and of these only 58 are accepted as authentic.
2. Syphilis of the bladder is not so rare as the comparatively meager literature on the subject would seem to indicate.
3. Bladder syphilis would probably be more frequently recognized if more frequently looked for.
4. All cases of hematuria and pollakiuria should be looked upon with suspicion until found to be of other than syphilitic etiology.
5. There is nothing characteristic either in the symptomatology or the cystoscopic picture of bladder syphilis, so the diagnosis must rest upon other evidence.
6. The prognosis of syphilis of the bladder is good.
7. The treatment is specific.

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LATE SYPHILIS OF THE RECTUM

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TERTIARY syphilitic changes such as ulcers, gummata and fibrous hyperplasia in the rectum arise sometimes very late in the disease, often after all of the earlier evidences have disappeared. They cause most distressing changes which are likely to be mistaken for tuberculosis or cancer. An indurating edema which is associated with these changes further complicates.

MacCallum¹ says, "It will be observed in considering the development of the tertiary syphilitic lesions that they often arise in places where there were secondary lesions which had healed, and it has been suggested that they are the effect of the further growth of spirochetæ which had been left behind in the healing of the secondary syphilis. The evidence is not entirely convincing in regard to this, although there are many well attested cases in which gummata appeared on the site of secondary lesions."

Gummata occur quite frequently in the rectum and may be single or multiple although Johnson² says the isolated gumma is very rare. It may develop in the mucosa of the anus or rectum, in the connective tissue of the bowel or of the ischiorectal fossa. It is painless, usually the size of an enlarged lymph gland, but may attain an enormous size. By digital examination the mass feels like a uterine myoma or if several gummata exist and they are small, they feel like peas or marbles beneath the mucous membrane. An area of fibrous hyperplasia extends about the gumma and radiates out into the normal tissue. Thus the growth closely resembles early cancer by being nodular and freely movable in the submucous connective tissue. Later a caseating necrosis develops in the center of the gumma and the tumor becomes soft and elastic. As the tumor enlarges it projects into the lumen of the bowel and is exposed to trauma and ulceration. The gumma does not abscess or extend in chains and is thus differentiated from an infected lymph gland.

Case C-23 presents a large single gumma. This woman, a seamstress, aged 40, had not been able to work for a year because of pain in the rectum. She has

daily bowel movements which are streaked with blood or mucus, but the evacuations are not particularly painful. She has not lost weight. On digital examination is found about two inches above the anus a large, hard, round, lobulated tumor about two inches in diameter. It is between the rectum and the coccyx and is firmly fixed. It is not painful and may easily be mapped out. No fluctuating spots are found. An x-ray photo clearly shows the growth. A clinical diagnosis of gummata was made and under treatment it promptly showed improvement (Fig. 1).

Softening and liquefaction of the gumma later occurs with rupture into the rectum. Fecal matter is forced into these pockets and thus ischiorectal abscesses are formed, many fistulæ may thus appear extending out onto the skin or invading the bladder or vagina. If a gumma is incised the wound remains unhealed and later becomes surrounded with extensive, dense scar tissue. Finger and Landsteiner³ have shown that gummata contain living spirochetæ which can produce infection in another animal.

The proctitis associated with the ulceration and cellular infiltration occasions a mucopurulent discharge, a feeling of fullness in the rectum and sphincteric tenesmus. When ulceration is marked a deep burning pain is complained of. Each defecation is painful and is usually followed by bleeding.

Fibrous infiltration of the rectal coats without distinct gumma formation but instead a diffusing through all the structures of the bowel, particularly, the mucosa and submucosa, sometimes occurs. Multiple syphilitic nodules arise in the mucous membrane, usually just within the rectum proper, and spread upwards sometimes as far as the sigmoid flexure or colon. This is a hyperplastic proctitis, a diffuse and wide infiltration of the whole wall of the gut but especially the submucosa, with mononuclear and epithelioid cells. It soon breaks down into extensive ulcers which may even surround the rectal lumen. A foul discharge is present and defecation is painful. Numerous fistulæ develop, some of which extend widely out on the buttock into the vagina or urethra. Pain and tenesmus are constant because ulceration is extending in one place while cicatrization goes on in another. Alternate constipation and diarrhea occur and the rectum is dilated and hypertrophied above the ulcerated area. Later the dense scar formation about the healing constricts the lumen of the gut and obstruction arises. Although

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Fig. 1.—Gumma of the rectum. A. Location of the gumma.

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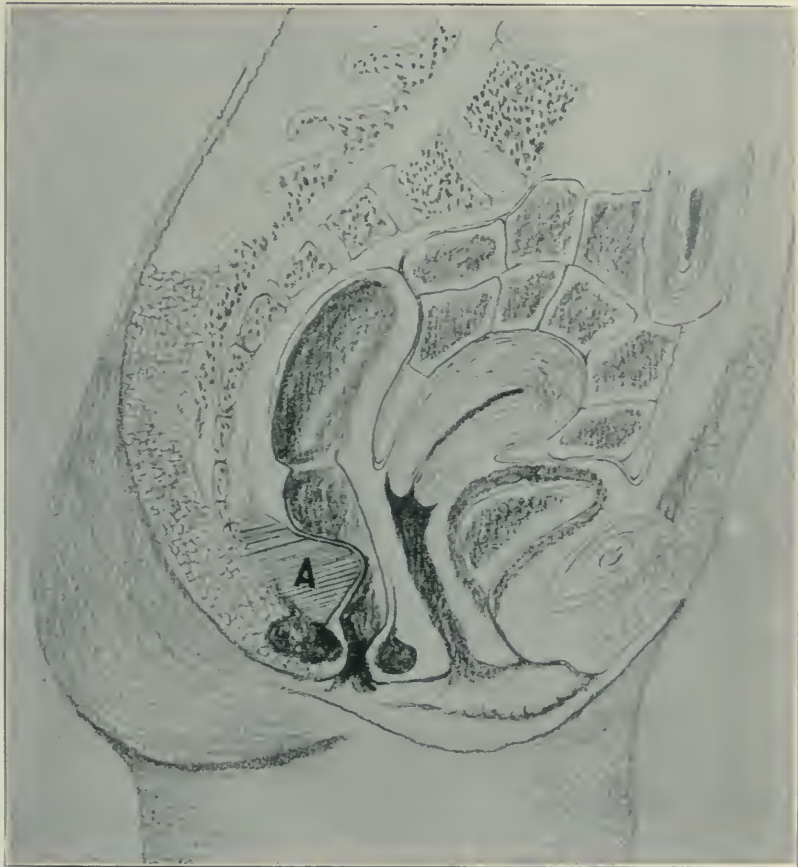


Fig. 2.—Schematic section of pelvis showing location of the gumma.

this condition is very exhausting the patient usually dies of some other cause for which this chronic poisoning prepares the way.

CASE 1.—A woman, aged 42 years, married, two children, no history of syphilis. About three years ago she noticed a hardness of the perineal body. The vagina seemed hard and stiff, her physician gave her local treatment without success. When I saw her she suffered from obstinate constipation which was gradually getting worse and a tentative diagnosis of carcinoma had been made. On examination the anus was found in its normal position. The skin of the perineum and about the anus was rough and wrinkled, dry and thickened, but not sensitive. On attempting a digital examination I found the rectal wall hard, rough and tight about the finger, making introduction very painful. The narrow, cylindrical three-quarter inch rectoscope was introduced with difficulty and the bivalve could not be satisfactorily opened. The hardness and fullness of the tissues was greatest at the anus and shaded away for a distance of five inches within the rectum. The examination was painful and although it stretched the tissues considerably it did not cause any bleeding. I removed three pieces for microscopic examination and the clipping caused very slight bleeding which was easily and promptly checked.

SYPHILITIC STRICTURE OF THE RECTUM

Just how frequently syphilis causes stricture of the rectum is a mooted question. Some authors claim that all nonmalignant strictures are syphilitic, while others are equally positive that strictures result from any ulcerative changes regardless of its type or etiology. At any rate we do find that syphilitic stricture may follow any syphilitic ulcer as chancre, secondary ulcer or broken down gumma and that it has certain peculiar characteristics. The Wassermann reaction will, however, help us to decide definitely for or against lues in a given stricture. Clinically, however, it is sometimes impossible to say that a given stricture is or is not syphilitic. Of course once ulceration occurs and septic infection is added the picture is so confused that a microscopic examination of a piece of the tissue may be necessary for diagnosis. The chancroid though not syphilitic, is a close cousin and frequently produces a very serious form of stricture.

The discharge of blood, mucus or pus of which many syphilitics complain during the secondary stage is often attributed to the mercuric remedies administered and the probability of the presence of mucous patches or ulcers is forgotten. We do not see stricture patients during the latent or infiltrating stage because they do not consult a physician until they are suffering from stenosis of the rectum. Histologically we find in the syphilitic stricture a chronic

inflammatory formation about the blood vessels and within their walls. Especially is this found in the arteries. This obliterating endarteritis is the same as found in any syphilitic lesion.

The infiltration and thickening of the mucous membrane about the ulceration or about the minute gummatous deposits in the mucous membrane imparts a stiff, rough leather character to the rectal wall and thereby limits and lessens the distensibility of the rectum. A sanious or mucopurulent discharge fills the rectum. Later when the ulcer may have healed the mucous membrane remains dry. The cicatrix is blue-white, dense and hard and usually presents some ulceration at its upper extremity. Syphilitic ulcers are inclined to follow the course of the lymph and blood vessels and as that direction in the rectum is lengthwise the contracted portion is usually tubular instead of sharply annular as we find in the inflammatory stricture. This condition may extend from the anus to the colon although most syphilitic strictures occur from 1 to 3 inches from the anus. The more recent part of the stricture with its infiltration and proliferation is frequently the most obstructive. Ulceration may also be found below the stricture and from these ulcers fistulæ lead to perirectal abscesses or open externally on the skin or into the vagina or urethra.

When decided stricture occurs low in the rectum constipation alternates with diarrhea and the passage of ribbon shaped or broken stools.

Prognosis.—Prognosis is guarded. Even though the lesions are cured by medicinal treatment the atrophy of the sphincter frequently produces fecal incontinence.

As has been mentioned above, some of the obstructive symptoms result from the inflammatory swelling about the ulcers. This infiltration and swelling of the mucosa is not syphilitic, but rather a reaction to the local streptococcic infection. As the luetic endarteritis subsides gummatous deposits resolve or the ulcers heal under treatment, the swelling of the mucosa lessens and sometimes the obstruction is relieved. Case C-5 presents such a condition: About one year ago this woman began to have constant pain, of a cutting character, in the rectum, with rectal tenesmus. Since then she passes blood and pus almost every day. During this time she lost fifteen pounds in weight. She is 26 years old. A positive Wassermann was obtained. She was placed on antisyphilitic medication

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Fig. 3.—Typical syphilitic stricture of the rectum.

and immediately began to improve. She had formed fecal passages, her pain disappeared and her appetite returned. Nothing surgically was attempted and in the midst of our treatment she disappeared.

Differential Diagnosis.—The differentiation of syphilitic from malignant strictures is a most important factor. Syphilitic strictures usually are long, funnel-shaped contractions with blue-white cicatrices about the ulcers. The edges of the ulcer are never undermined but rather crater-like.

Fig. 3 shows the tightly contracted rectal lumen of a syphilitic stricture. This woman, Case C-8, contracted syphilis seven years ago. For the past year she has had pain in the rectum and a purulent sanious discharge. Bowels are always constipated. On digital examination the finger at a distance of one and one-half inches from the anus comes to a solid impassable stricture. The rectum below the stricture is hard and nodular. The patient has several fistulæ leading into the vagina and others out onto the skin. These are tender as the digital examination is made. The patient has been on intensive antisyphilitic treatment for some time and although her general condition has much improved the obstipation is still a serious matter and an abdominal anus has been advised.

Not all syphilitic strictures are long and pencil-like in character. Sometimes the pathology is limited to a small area and the stricture is more annular in character as in Fig. 4. Here the differential diagnosis from the physical findings was not possible before operation. At operation, however, the extra colonic hyperplasia was found limited to one side of the bowel and subsequent microscopic examination excluded carcinoma.

CONGENITAL SYPHILIS

Many of the manifestations of congenital syphilis appear about the anus of young infants and may be overlooked or mistaken for simple skin irritations due to lack of cleanliness. The earliest manifestations of syphilis in babies is an erythema or dermatitis about the anus accompanied with shallow fissures. The anal mucous membrane also is fragile and brittle and the fissures are easily produced by dilating the anus. If untreated the ulceration spreads. The skin surface becomes copper-colored and later is thickened and

raised and emits a thin, seropurulent and very fetid discharge. The little fissures may extend into the anal canal and may be secondarily infected. As these ulcers or fissures heal they leave radiating scars (so-called rhagades). All of this change may occur within the first few months of life. It may begin within the first week or may not evidence itself until the baby is two months old, and may be mistaken for the chafing that results from contact with feces and urine but the latter condition is never associated with the numerous small, shallow anal fissures found in syphilis.

TREATMENT OF TERTIARY SYPHILIS

The treatment of tertiary syphilis of the anus and rectum requires special management of the local conditions. Every effort must be made to prevent septic infection. The patient should be put to bed and the bowels moved regularly and also irrigated. Ulcers should be cauterized. If the ulceration is extensive and the discharge profuse, the sphincters should be dilated to assist drainage.

The systemic treatment consists in the administration of full doses of potassium iodide, preferably given in milk or essence of pepsin, the dose built up to 60 to 100 grains daily in small, frequently repeated doses. Mercury should be exhibited by inunction or by hypodermic, because when given by mouth it sets up a teasing diarrhea. Hypodermically, I think, I have had the best results with salicylate of mercury. Every patient should also be given a course of intravenous treatment of arsphenamine.

Locally, ulcers should be carefully and persistently treated. Daily dilating does much to reduce the local capillary congestion, but it must be carefully performed for fear of lacerating the mucosa or even tearing through the bowel wall. These strictures must not be cut as they invariably fill up with granulations which contract further. Their pathology is not wholly syphilitic but has added septic infection and posterior proctotomy, excision of the diseased field, or the construction of an abdominal anus may be necessary.

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A MORE RAPID AND IMPROVED METHOD OF
DEMONSTRATING SPIROCHETES
IN TISSUES*

(WARTHIN AND STARRY'S COVER-GLASS METHOD)†

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THE best method yet devised for the demonstration of the *Spirochete pallida* in tissues has unquestionably been that of Levaditi, particularly, in our experience, Warthin's modification of this method (*Bulletin No. 6 of the International Association of Medical Museums*). Levaditi's original method requires at the very least seven days, usually ten days. Warthin's modification requires about fourteen days. Levaditi's method treats the tissue *en masse*. Aside from the length of time required, the staining in tissue-mass constitutes a very great disadvantage. It is impossible to locate active syphilitic infiltrations and then apply spirochete staining by this method; consequently the search for the spirochete often becomes a needle-in-the-hay-stack affair, with hundreds or thousands of sections to be examined, too often fruitlessly. It has been necessary to take neighboring blocks, one for the spirochete method, the other for ordinary stains, in the attempt to check up the relationship of the spirochete to the tissue lesions. In practical diagnostic work this disadvantage has been a serious handicap. When active syphilitic lesions, or suspected syphilitic areas, have been found in sections taken from a paraffin block and stained with hematoxylin and eosin, it has hitherto been impossible to apply successfully any of the spirochete methods to other sections taken from the block in the attempt to determine the association of spirochetes to such lesions. The only recourse has been to take the paraffin out of the block, run the tissue back through xylol,

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alcohol and water, and then to carry it through the full Levaditi method. This we have accomplished successfully in some cases; but in others failure results. Moreover, even in expert hands the staining *en masse* gives varying and capricious results, with a too-high proportion of failures. Some laboratory workers are unable ever to obtain satisfactory results with the Levaditi method; and there can be no doubt the time required for the Levaditi method and the difficulties attending it have been so discouraging to the average technician that very few diagnostic pathologic laboratories are making any effort to use the demonstration of spirochetes in tissue as the diagnostic aid it should be. The method is said to be too capricious, too difficult and too time-consuming; therefore it is not used.

What is sorely needed is a method of demonstrating spirochetes in tissue *in sections stained singly*, taken from tissue-blocks so treated that all ordinary stains may be used if desired. This would permit the application of the spirochete method to localized lesions discovered in the routine staining methods. The time must be greatly shortened, ordinary fixations made applicable if possible, and the elements of capricious results avoided. We have for some time been carrying on systematic investigations in the search for a method of this kind, under a grant given this laboratory for this purpose, by the Interdepartmental Social Hygiene Board. In this work we have already hit upon several new methods of importance; and while continuing our researches for still more ideal methods, we are presenting here a method of demonstrating spirochetes in sections mounted on cover-glasses, that in our experience is far better than the old Levaditi method. It has the following advantages.

1. Ordinary formol fixations will give good results. Alcohol fixations also succeed.
2. The sections can be stained singly, on cover-glasses.
3. Time is much shortened; three days are sufficient.
4. Results are more certain than with the Levaditi.

The outline of the method is as follows:

(Warthin and Starry's Cover-glass Method for Demonstrating
Spirochete pallida in Sections)

1. Tissue fixed in neutral formol (4 per cent) or alcohol for one to three days. Ordinary routine formol solution will do.

2. Wash thoroughly in distilled water to remove all traces of formol.

3. Imbed in paraffin (alcohol, xylol, paraffin).

4. Cut and mount sections on cover-glasses with albumin fixative.

5. Remove paraffin (xylol, alcohol, water).

6. Place cover-glasses in a saturated solution of ferric alum, or a 4 per cent solution of ferrous ammonium sulphate. Keep in incubator one to two hours.

7. Wash in distilled water.

8. Rinse cover-glass and section in a 2 per cent silver nitrate solution. Cover section with another perfectly clean cover-glass which has also been rinsed in the silver solution. The cover-glasses will be held together by capillary attraction. Place them carefully on the bottom of a bottle of silver nitrate solution. Bottle should be covered with black paper. Cork tightly, and place in incubator for three to twenty-four hours.

9. After impregnation pour off the silver nitrate solution, and rinse in distilled water without removing cover-glasses from bottle. Pour water into bottle, shake gently a few times and then pour off.

10. Pour reducing substance (pyrogallie acid, 4 grams, 40 per cent formol, 5 c.c., distilled water, 100 c.c.) into bottle. See that fluid passes between cover-glasses, by pressing upon cover-glass with glass rod, or by shaking. Reduction must occur uniformly over the section or brown lines will result. Reduction is usually instantaneous. Remove section after two to three minutes, wipe off any brown or black precipitate on the albumin fixative about the section with a cloth, taking care not to touch the section.

11. Wash in distilled water.

12. Absolute alcohol, xylol, balsam.

GENERAL CONSIDERATIONS

Best results are obtained when the fresh tissue is cut about 5 mm. thick before fixing. Four per cent neutral formol is perhaps the best fixing fluid. All formol must be washed out, for it is a reducing agent and if present will interfere with the silver impregnation. After thorough washing the blocks go into 96 per cent alcohol, in which they may be kept for any desired length of time, or the

tissue may be run as usual into absolute alcohol, xylol, and imbedded in paraffin.

Sections of the paraffin blocks should not be thicker than 5 microns. Great care should be taken in mounting the sections on the cover-glasses. Three-quarter inch, No. 1 or thin No. 2 covers should be used. A small drop of albumin fixative is placed on the clean cover-glass and thoroughly rubbed over the surface, removing excess by repeatedly rubbing the ball of the finger over the cover-glass and each time wiping off the finger on a clean cloth. By repeatedly rubbing the cover-glass with the dry finger in this way a minimum of albumin fixative is left on the cover-glass, so that there is not a sufficient amount of it to interfere with the silver impregnation. If too much albumin fixative is left on the cover it becomes stained. The properly smeared cover-glasses are placed on clean cardboard, covered with clean paper and kept in the incubator for twelve hours before they are used. They should not be dried over a flame, as this usually results in scorching or incomplete drying, so that the sections float off later.

The sections should not be thicker than 5 microns, preferably 2-3 microns. As they are cut they are floated on warm water that has recently been boiled to prevent bubbles forming on the under side of the section. As the sections flatten out they are caught up on the prepared cover-glasses, the water blotted off, and the cover-glass warmed over the flame until the paraffin begins to melt. They are then placed in the drying oven for two hours, when they are ready to stain.

The staining process should be carried out, as far as possible, in the dark. Brown bottles with wide mouths should be used. These should be covered with black paper, and should have tightly fitting corks.

Remove the paraffin from the sections on the cover-glasses by means of xylol. Remove xylol with absolute alcohol. Then wash cover-glass preparations thoroughly with distilled water to remove all traces of alcohol. Then transfer cover-glasses to a saturated solution of ferric alum or a 4 per cent ferrous ammonium sulphate for one to two hours in the oven, covering staining dish to prevent evaporation and precipitation of dust on the sections. Wash thoroughly in distilled water. (The treatment with iron salts can be given the

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Fig. 1.—Photomicrograph of *Spirochete pallida* in section from hard chancre, made from ordinary diagnostic block after sections had been examined in hematoxylin and eosin. Tissue had been sent to laboratory rolled up in gauze moistened with formalin. Spirochete stain obtained twelve hours after histologic examination.

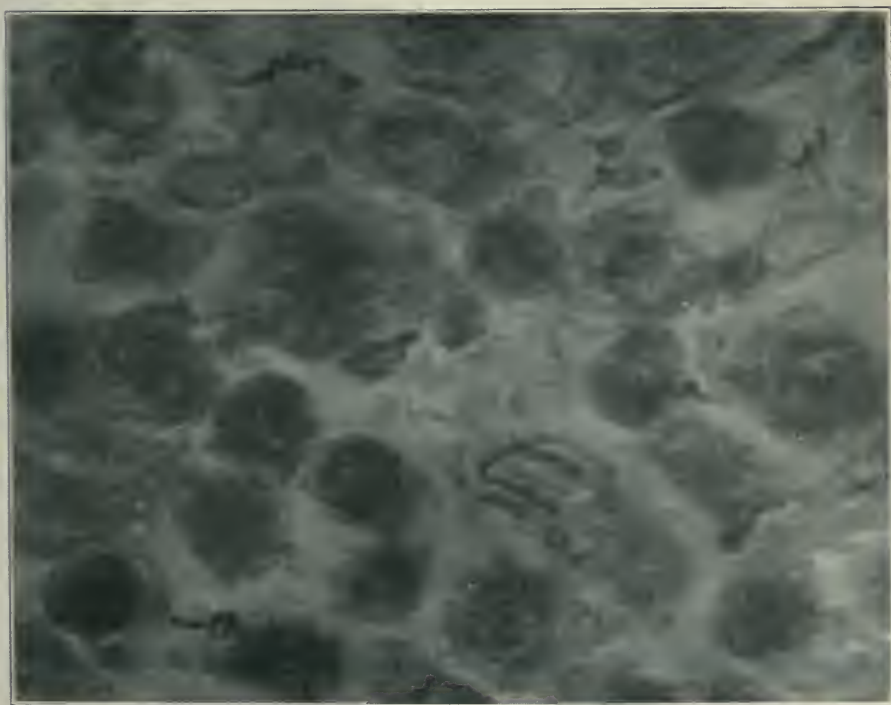


Fig. 2.—*Spirochete pallida* in syphilitic tonsil. Tonsil had been given routine fixation in 4 per cent formaldehyde solution. Sections stained with hematoxylin and eosin showed the histologic changes regarded by Warthin as syphilitic. This photomicrograph was made from a section obtained from the same paraffin block, stained by the new method within twelve hours.

block of tissue before imbedding, in the oven eight to twenty-four hours, according to the size of the blocks.)

After washing, the cover-glasses are put into the silver nitrate solution in the bottles. A 2 per cent solution of silver nitrate is used; it should be made fresh each time, as stock solutions do not give good results. Ten to 20 c.c. of the solution is sufficient for each bottle. Rinse the cover-glass with the silver solution, place on it another clean cover-glass rinsed in the same silver solution. They are held by capillary attraction, and are then placed carefully on the bottom of the bottle, which is tightly corked, and then placed in the oven, twelve to twenty-four hours giving the best results, although fair stains may be obtained at three hours. After impregnation the silver nitrate is poured off, and the cover-glasses rinsed in the bottle with distilled water. The cover-glasses need not be removed from the bottle. The water can be poured into the bottle, which is shaken a few times to insure thorough washing. The water is then poured off, and the reducing substance poured in.

Pyrogallie acid, in the same solution as used for the Levaditi method, makes a good reducing substance.

Pyrogallie acid	4 g.
40 per cent formol	5 c.c.
Distilled water	100 c.c.

A gallic acid solution may also be used. To a 2 per cent gallic acid solution add, drop by drop, a 1 per cent NaCO_3 solution, until a drop of the mixture added to a silver nitrate solution causes instant reduction.

The reducing fluid must pass quickly between the cover-glasses. This can be accomplished by applying pressure to the upper cover-glass at the bottom of the bottle or by gently shaking the bottle. If the reducing substance does not pass over the section at an even rate brown lines will be produced wherever the flow stops from the too great reduction of silver nitrate at this point. The reduction should be instantaneous over the whole surface of the section, but it is best to leave the cover-glasses in the reducing fluid for two to three minutes. There may be a brown or black precipitate on the albumin fixative about the section; this should be rubbed off with a clean cloth, care being taken not to touch the section with the cloth. The reduced section should have a faint, dull brownish

yellow color. A bright yellow color indicates poor staining of the organisms. As soon as the cover-glass is cleaned the preparation is washed in distilled water, dehydrated in absolute alcohol, cleaned in xylol and mounted in balsam.

The trick of this method is the application of the silver nitrate solution and the reducing substance in *small mass action* between the cover-glasses. The uncovered section can not be successfully treated with silver and reducing solutions, it becomes too black and the precipitate covers up everything. If the cover-glasses become separated in the silver solution during impregnation the section will become covered with a black precipitate. By this capillary attraction method of treatment a minimum amount of silver and reducing substance is admitted so that the spirochetes become more heavily impregnated than the tissue, and are easily seen. They have a deep reddish brown color contrasting sufficiently strongly with the yellow background, as is clearly shown by the two photomicrographs, the sections of which were taken from ordinary tissue blocks in the routine laboratory diagnostic service. The histologic lesions of these, one a chancre, the other a tonsil lesion, were first recognized in the hematoxylin and eosin stains. Taken from routine diagnostic material, these tissues were poorly fixed rather than well fixed. The chancre had been sent to the laboratory by mail; it had been wrapped in formol-soaked gauze, at least two days before arrival, and was then accorded ordinary routine rapid fixation. After the recognition of the histologic lesions it took but twelve hours to demonstrate the spirochetes. As far as time and technical considerations are concerned this is, therefore, a very great improvement over the Levaditi method. Moreover, control series with this method and with the Levaditi, show a much greater element of certainty with the cover-glass preparations. It is much less capricious. The method is not difficult, if directions are intelligently followed. Untrained laboratory workers and students have had no trouble in getting well-stained spirochetes the first time. Results will vary, probably due to slight differences in physical conditions and in washing. More silver nitrate may be washed out between the cover-glasses in one case than in another. If the section turns out a bright yellow the spirochetes are usually not well stained or do not show at all. When the section has a dull, faint color the indications are for well-

stained spirochetes if they are present. Ordinarily the reticulum stains as the other tissue elements, but even when of a deeper brown tone it does not interfere with the search for the spirochetes. The use of the iron salts seems to inhibit staining of the tissue, and brings out the organisms more clearly. By treating the tissue with iron salts the organisms can be stained in tissues fixed routinely with formol or alcohol; and it becomes possible to demonstrate them when the Levaditi method fails. The chief differences in appearance between the cover-glass preparations and the Levaditi ones, are the dark reddish brown color of the spirochetes, the less deeply stained tissue and less abundant precipitate of the former. The spirochetes are never as black as with the Levaditi, but the photomicrographs (taken with a color screen) are as good as those obtained by the latter method.

The successful operation of this new method consists in a trick of producing certain physical conditions between two cover-glasses, with a minimal amount of reaction between the tissue and the silver and reducing solutions, so that the spirochetes are more deeply stained than the tissue-elements, and precipitates are avoided. The use of iron salts favors the differential staining of tissue and spirochetes. When the knack of using this method is acquired, and it is very easily acquired, sections from routine diagnostic blocks can be used, much time can be saved, and results seem more certain. It is, then, a great improvement over the old Levaditi method or any of its modifications. We do not, however, believe, that we have yet found the ideal method for which we are searching, and our investigation will continue in the hope of achieving it.

JUVENILE PARESIS

By EDWARD LIVINGSTON HUNT, M.D., NEW YORK CITY

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THERE are six types of paresis—the simple dementing, the simple depressed, the agitated, the irregular or taboparetic type, the classical or expansive type, and finally, juvenile paresis. It is to the latter type that I wish to call your attention, mentioning its symptomatology, clinical signs, importance, and occurrence, and report to you a case which I have observed.

An unusual feature in this case is the variability of the colloidal gold curve during the past six months. The case is unusual in that the curve began as a meningitic, then progressed to a typical luetic, and finally at the end of a few weeks developed a perfectly straight-forward and typical paretic curve.

Juvenile paresis is a type quite distinct from all the others and stands apart. Clouston was apparently the first to recognize it describing a case as far back as 1877. Since the appearance of the Wassermann test, and the still more modern colloidal gold reaction, its appearance has been more frequent and reports of cases are yearly becoming more numerous. The greater frequency of these cases is undoubtedly due to the diagnostic aid which the colloidal gold reaction offers. It really is the only positive and definite means of diagnosing this particular type, as the clinical picture is one which varies greatly. When, in addition to this, one considers that many of these cases of juvenile paresis occur in infants and young children who are backward, one realizes how exceedingly difficult it is to differentiate the cases of juvenile paresis from those of backwardness, imbecility, and cerebral atrophy.

One of the characteristic features of these cases is the fact that the child may develop in a perfectly normal way for the first few years of life, giving no suspicion as to the future appearance of a paretic condition. If the disease develops later, or in the early teens, the mental drop is more apparent, more acute, and more rapid. The younger children gradually deteriorate. At first the change in mentality, morale, and physical condition is scarcely apparent,

so gradual is the progress of the condition. The disease becomes fairly well developed before the parents or physicians are aware even of its presence. So many infantile conditions occur which illustrate the symptoms of juvenile paresis, such as the convulsions of epileptics, the excitability and depression of neurotic children, the childishness and backwardness of the constitutional inferior, that the diagnosis is obscure.

The mental symptoms of juvenile paresis are defective memory, dementia, excessive childishness, and a tendency to fabricate. This fabrication is undoubtedly a symptom of impaired morality. These children not only lie but embellish and enlarge their stories. Added to these symptoms are alternating periods of exhilaration and depression, fears, and anxieties.

The physical symptoms resemble those occurring in the adult form, such as tremors, exaggerated reflexes, and immobile and unequal pupils. In each type occur convulsions which are epileptiform in character. They are, however, much more common in the juvenile forms. In this latter type the convulsion marks the early stage, whereas in the adult type it marks the later. The convulsion is one of the principal points of confusion between idiopathic epilepsy and juvenile paresis. The mistake should not be made of placing every convulsion occurring in childhood in the class of teething or epilepsy. The almshouse, nurseries, and epileptic colonies are today sheltering many juvenile paretics under the misnomer of epilepsy and defective teething.

These latter symptoms appear as the ordinary clinical manifestations in many mental disorders. Inasmuch as paresis is so protean a disease it is only natural that it should display the many varied symptoms which appear in numerous mental disorders. Just as paresis has various pupils and various reflexes and tremors, so does it show various mental symptoms. The lesion in paresis is multiple, and therefore, the symptoms, both physical and mental, are multiple. It may present many varied forms. No two cases are exactly alike. No definite classical type can be described, and no form or clinical type can be used as a standard. One should be prepared to see almost any development in paresis, physical or mental.

In one case exhilaration or depression may predominate, in another phobias, or anxieties. One must, therefore, be constantly on the alert, and no correct diagnosis can be made until paresis

has been eliminated. This holds just as true of juvenile paresis as of the adult form. In fact, I think it is more apparent and of greater importance in the younger than in the older type.

My reasons for emphasizing these points are five in number. In the first place, the patients are too young to warrant forming a complete or just conception of their mentality. Second, the patients are too young to express and give definite form to their delusions. Third, the patients are too young to have acquired syphilis. Fourth, the general practitioner is ignorant of the occurrence of juvenile paresis and therefore not on the alert for it. Fifth, the symptoms of juvenile paresis are similar to those of other infantile conditions.

The pathology and the histopathologic changes of the juvenile type are identical with those of the adult form and need take no time in the present discussion. These changes in paresis are so well known by us that I shall pass them by.

The age of juvenile paresis is usually about ten or twelve. The reason for this one can readily understand when he stops to reflect that a certain period of time must elapse between the acquirement of the syphilitic infection and its full development into the parietic form. In the adult this period of time extends anywhere from seven to twenty years. In the child the same rule applies. In the child, of course, the lesion is not acquired, but hereditary, and therefore, the length of time must date from birth. This would necessitate the development of the disease about the tenth year. One of the leading symptoms of juvenile paresis, a condition more marked in the young than in the adult, is the degree and rapidity of physical emaciation and exhaustion. Children afflicted with this condition appear to have less resistance and therefore disintegrate more rapidly. Again, the course of the disease is shorter, four years being about the maximum time.

The following case to which I wish to call attention, entered St. Luke's Hospital last December, and was placed on the service of Dr. Farnham Collins, the attending pediatrician. In my capacity as neurologist to the hospital, I was enabled to see and follow the case and I am indebted to Dr. Collins for allowing me to report it. I shall give you the history, call your attention to the clinical symptoms, the course of the disease, and especially to some unusual forms

which the colloidal gold curve assumed, and finally to the difficulty which we had in giving salvarsan to this patient.

Patient came into the hospital on December 21, 1917, at the age of seven, complaining of convulsions. The previous history showed that ten months before the child had developed headaches and one month later had her first convulsion which affected the left side. At that time there were severe twitchings in the left leg and arm. After this she improved until one month later she developed her second convulsion. Following this she had one every month. About last November the convulsive movements attacked for the first time the right side. After this she was unable to speak. A second convulsion involving the right side followed two days later.

After the first convulsion, the child was irrational and garrulous until the convulsion occurred which affected the right side and therefore the speech center of the brain.

The previous history was negative except for measles and a rash and sore mouth at three months. These two latter might have been due to a mouth infection. The family history showed that the mother had one miscarriage, and that the father was a syphilitic.

The physical examination made upon entrance to the hospital is as follows: "The child is well nourished but gives the appearance of being chronically ill; does not talk but appears to understand; the scalp and ears are O. K.; the pupils are dilated but sluggish in their reaction to both light and accommodation. The nose is negative; the mouth is in poor condition, with an infection of the teeth. In the neck there are enlarged glands in the front, beneath the jaw. The chest, heart, and abdomen are negative. The lungs show fine rales. There is a slight papular eruption on both forearms and back. The knee jerks are overactive." The diagnosis made on admission was tertiary congenital syphilis. The temperature ranged between 98 and 99, the pulse between 97 and 100. The Chic test was negative. The von Pirquet test was also negative. On December 24, the blood Wassermann was four-plus. On December 26, a lumbar puncture was made which showed the presence of fifteen cells, 100 per cent lymphocytes, and a positive Wassermann reaction. The colloidal gold curve was as shown in Chart I.

On January 12, 1918, 0.4 grams of salvarsan was given intravenously. Forty minutes later 30 c.c. of blood was taken for an intraspinal injection. On the following day, a lumbar puncture was made a second time, and 10 c.c. removed under normal pressure. The cell count was 150; the spinal fluid Wassermann 4 plus; the differential count showed 80 per cent lymphocytes, 20 per cent red blood cells, and a positive butyric acid reaction. At the same time 5 c.c. of salvarsanized fluid was injected intraspinaly. The colloidal gold test of this puncture was as shown in Chart II.

On January 16, three days later, the child was brighter and recognized her father, shook hands, and said "No." On January 24, 1918, 0.4 grams of arsenobenzol was given intravenously, and one hour later 60 c.c. of blood was withdrawn from the same vein. On the following day a lumbar puncture was made, 18 c.c. were withdrawn under decreased pressure, and the same amount of arsenobenzol serum was given intraspinaly. The cell count was 8, the differential

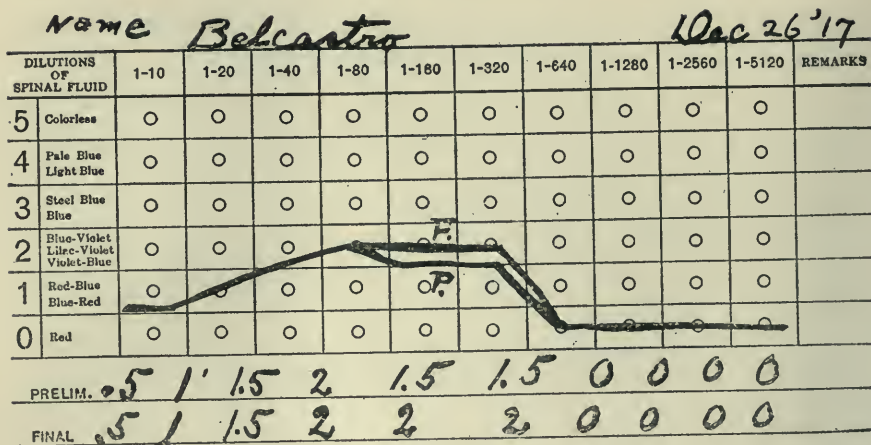


Chart I.

count was 100 per cent, the butyric acid test was negative, and the Wassermann reaction on the spinal fluid was 4 plus. The colloidal gold curve is illustrated by Chart III.

On February 18, 1918, another lumbar puncture was made, the fluid being under slightly increased pressure. Eight c.c. were removed, the cell count was 6, the differential count 100 per cent, the butyric acid reaction 0, the spinal fluid reaction 3 plus. The colloidal gold curve is shown in Chart IV.

On February 28 the lumbar puncture resulted in 5 c.c. of fluid under normal

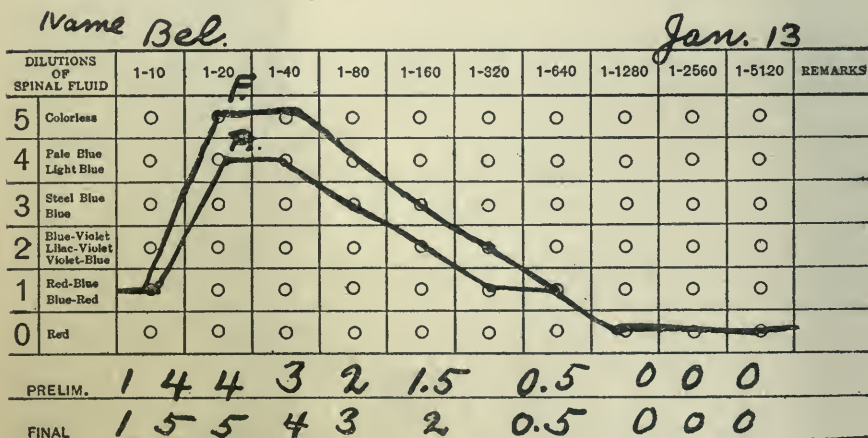


Chart II.

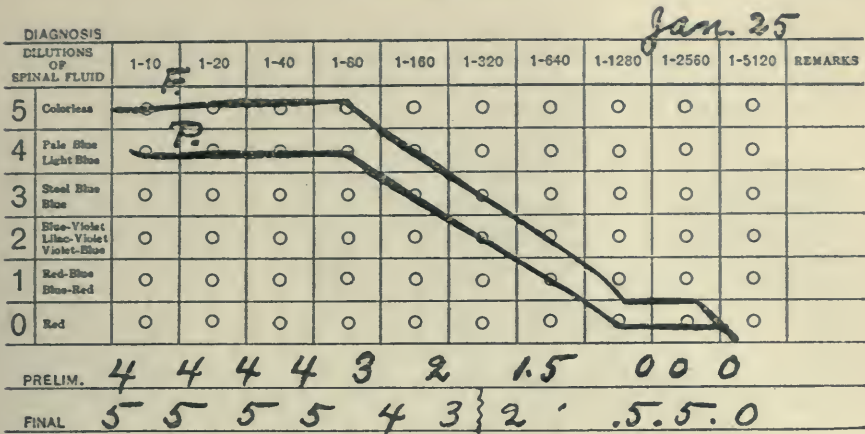


Chart III.

pressure, with a cell count of 5, the differential count of 95 per cent and a plus butyric acid reaction. The colloidal gold curve is illustrated in Chart V.

The child died the 12th. of March. No autopsy was performed. The points which I wish to bring out in this child are first the temporary improvement following the intraspinal injections. Secondly, and especially, I wish to bring out the variability of the gold curve. The first was a typical luetic curve, the second less so, the third almost a typical curve of paresis, the fourth less so, and the fifth even less. The diagnosis which was corroborated by the third and fourth gold curves was one of juvenile paresis. The case must have been in its incipency because the curves responded to treatment and finally colored down to one suggestive of lues, but by no means diagnostic of paresis. It is unusual to see in two

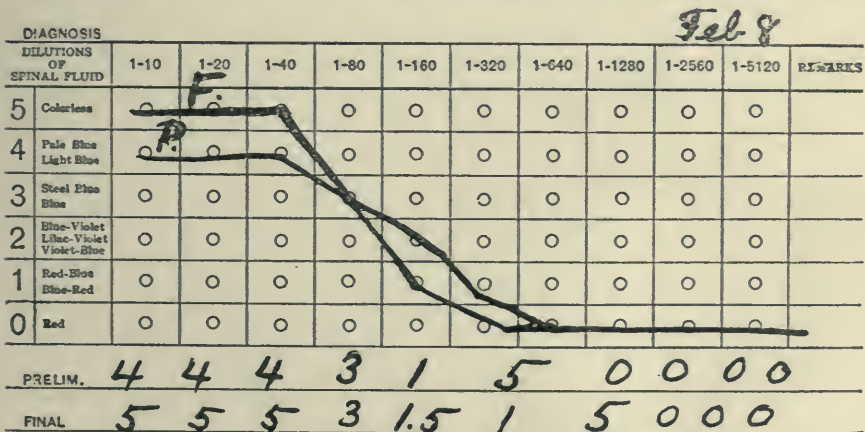


Chart IV.

months' time colloidal gold curves vary as much as these did. They are instructive because of the fact that a diagnosis should not be based on one curve and because of the fact that the gold curve varies and probably varies in accordance with the kind and extent of treatment.

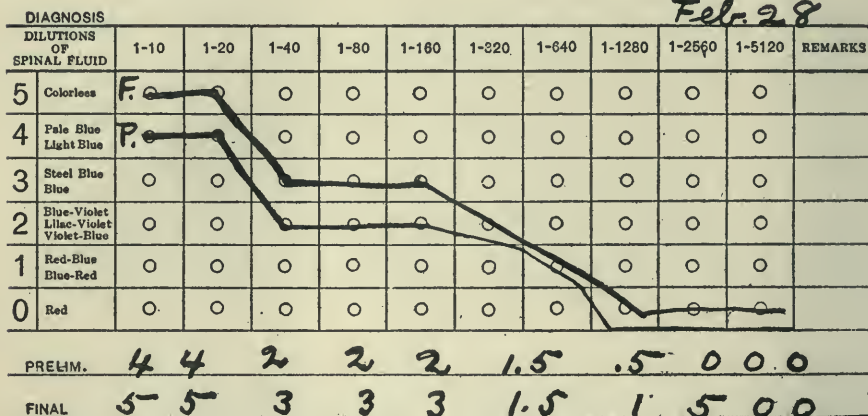


Chart V.

STUDIES IN THE STANDARDIZATION OF THE
WASSERMANN REACTION. VII

A STUDY OF THE NATURAL THERMOLABILE AND THERMOSTABILE
HEMOLYSINS AND HEMAGGLUTININS IN HUMAN SERUM
IN RELATION TO THE WASSERMANN REACTION*

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AS is well known, human sera contain hemolysins for the erythrocytes of various animals; owing to the widespread use of the antisheep hemolytic system, and since the great majority of sera contain hemolysin for sheep erythrocytes, this hemolysin has received particular attention and many serologists, particularly those who employ an antihuman hemolytic system, claim that the presence of these natural hemolysins may disturb quantitative relations in the hemolytic system to sufficient extent to reduce the sensitiveness of the complement-fixation test.

The presence and possible influence of hemagglutinins in human sera in relation to complement fixation have not received much attention; with the use of antihuman hemolytic system they are frequently encountered and as is well known, may prove sufficiently troublesome to constitute a drawback in the use of this system when clear cut hemolysis is desired.

In studies bearing upon the presence of natural hemolysins and hemagglutinins in human sera for the erythrocytes of the lower animals, no attention has been given the possibility of group hemolysins and agglutinins similar to the group of isohemolysins and hemagglutinins for human erythrocytes; as stated in a previous communication (1) we have found that these natural hemolysins and hemagglutinins for the erythrocytes of the lower animals in

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Investigation aided by funds accruing from the preparation of arsphenamine.

fresh human sera show grouping, and for this reason the percentages of these antibodies in human sera based upon work conducted with the corpuscles of one animal of a species, are only approximately correct.

PURPOSES OF INVESTIGATION

The presence of natural hemolysins and hemagglutinins in human sera have a relation to the subject of complement fixation in two main directions, namely, as bearing upon the properties of human serum as complement, and, secondly, in regard to the choice of a hemolytic system. The first mentioned relation has been considered in a previous communication¹ and it is the special object of this paper to consider the subject from the standpoint of the hemolytic system. Theoretically at least that hemolytic system is best which employs corpuscles for which there are no natural hemolysin or hemagglutinin in the complement serum or patient's serum to be taken into consideration; from the practical standpoint, however, the subject can not be dismissed so easily.

In this communication are given the results of our studies bearing upon the presence of hemolysins and hemagglutinins in unheated as well as heated human sera with special emphasis upon the presence of groups of these antibodies; as has been found in this study results based upon work with heated sera alone are not applicable to complement fixation tests conducted with active or unheated sera, and for this reason we have included a study of both as bearing upon the choice of unheated or heated serum for a standard technic. The actual influence these antibodies exert upon the Wassermann reactions has been the subject of special study and the results are given elsewhere.²

Part 1

THERMOLABILE AND THERMOSTABILE HEMOLYSINS IN HUMAN SERA

Inasmuch as most investigations on natural hemolysins have been devoted to that for sheep cells in heated human sera, it is commonly believed that natural hemolysins are thermostabile or heat resistant; on the contrary, many of these hemolysins are thermolabile and easily destroyed or inactivated during the process of heating serum prior to conducting the Wassermann test. A striking

example is met with an antiguinea pig hemolysin which is present in from 90 to 100 per cent of unheated and active human sera and in only 20 to 25 per cent of the same sera after heating at 56° C. for thirty minutes.

The nature of these thermolabile hemolysins is unknown; Thiele and Embleton³ regard the thermolabile hemolysins in active human sera as that for sheep erythrocytes, products of evolution from complement, whereas Sherman⁴ regards them as hemolysins which are "masked" by the process of heating without being actually destroyed, inasmuch as methods of absorption in his experiments revealed as much hemolysin in heated as in unheated sera. The results of our studies on the nature of thermolabile hemolysins⁵ have shown that as a result of heating sera at 56° C. for thirty minutes some of the hemolysins are actually destroyed and particularly antiguinea pig hemolysin, while others as antisheep and antiox hemolysins, are more resistant and tend to become "masked" or inactivated as described by Sherman, being still able to unite with corpuscles after the manner of an agglutinoïd.

The influence of heat upon natural hemolysins is shown in Tables I and II; apparently they vary in resistance. Antiginea pig hemolysin, for example, is usually destroyed or inactivated by heating for thirty minutes at 56° C. (Table I), whereas antisheep hemolysin is more resistant (Table II) at this temperature although usually completely removed when exposed to a higher temperature (62° C.) for the same period of time.

TABLE I
THE EFFECT OF HEAT UPON NATURAL ANTI-GUINEA PIG HEMOLYSIN IN HUMAN SERA

Serum	UNHEATED SERUM						SERA HEATED AT 56° C.*						SERA HEATED AT 62° C.*					
	CORP 1	CORP 2	CORP 3	CORP 4	CORP 5	CORP 6	CORP 1	CORP 2	CORP 3	CORP 4	CORP 5	CORP 6	CORP 1	CORP 2	CORP 3	CORP 4	CORP 5	CORP 6
C**	C	C	C	C	C	C	N	N	N	N	N	N	N	N	N	N	N	N
C	C	C	C	C	C	C	N	N	S	N	N	N	N	N	N	N	N	N
C	C	C	C	C	C	C	S	N	S	N	N	N	N	N	N	N	N	N
C	C	C	C	M	M	C	N	N	S	N	N	N	N	N	N	N	N	N
C	C	C	C	C	C	C	N	N	N	N	N	N	N	N	N	N	N	N
C	C	C	C	C	C	C	N	N	N	N	N	N	N	N	N	N	N	N

* For thirty minutes.

** C.=complete hemolysis; M.=marked hemolysis; S.=slight hemolysis; N.=no hemolysis.

TABLE II
THE EFFECT OF HEAT UPON NATURAL ANTI-SHEEP HEMOLYSIN IN HUMAN SERA

Serum	UNHEATED SERUM						SERA HEATED AT 56° C.*						SERA HEATED AT 62° C.*					
	CORP	CORP	CORP	CORP	CORP	CORP	CORP	CORP	CORP	CORP	CORP	CORP	CORP	CORP	CORP	CORP	CORP	CORP
	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
1	C**	C	C	C	C	C	C	C	C	C	C	C	N	N	N	N	N	N
2	C	C	C	C	C	C	M	M	S	S	M	S	N	N	N	N	N	N
3	M	M	C	M	C	M	N	N	N	N	S	N	N	N	N	N	N	N
4	C	C	C	C	C	C	M	S	C	M	C	S	N	N	N	N	N	N
5	C	C	C	C	C	C	M	M	C	S	C	S	N	N	N	N	N	N
6	C	C	C	C	C	C	C	C	C	C	C	C	N	N	N	N	N	N

* For thirty minutes.

** C.=complete hemolysis; M.=marked hemolysis; S.=slight hemolysis; N.=no hemolysis.

Inasmuch as sera for the Wassermann test are heated at 56° C. for one-half hour we have arbitrarily adopted this exposure for differentiating these hemolysins designating as "*thermolabile hemolysins*" those found in fresh unheated serum and as "*thermostabile hemolysins*," those found after the sera had been heated at 56° C. for one-half hour and reactivated by the addition of an adequate amount of hemolysin-free guinea pig serum complement. *All of these natural hemolysins, however, with the occasional exception of antisheep hemolysin are completely destroyed by heating at 62° C. for half an hour, whereas immune hemolysins suffer only partial deterioration at this exposure.*

THERMOLABILE HEMOLYSINS

Technic.—The majority of sera used in tests for thermolabile hemolysins, were derived from syphilitic persons and employed within forty-eight hours of the time of collection in doses of 0.05, 0.1 and 0.2 c.c. with 0.1 c.c. of 5 per cent suspensions of washed corpuscles. Sufficient saline solution was added to bring the total volume to 1.5 c.c. and incubation conducted in a water-bath at 38° C. for one hour followed by readings after standing in a refrigerator overnight.

Tests for group hemolysins were conducted with suspensions of erythrocytes from six to twelve different animals of the species under study; no attempt has been made to determine the number of

TABLE III

PERCENTAGE OF HUMAN SERA IN VARYING AMOUNTS SHOWING THE PRESENCE OF THERMOLABILE HEMOLYSINS FOR THE ERYTHROCYTES OF VARIOUS ANIMALS

HEMOLYSINS	SERA TESTED	PERCENTAGE OF SERA SHOWING PRESENCE OF HEMOLYSINS		
		0.05 c.c.	0.1 c.c.	0.2 c.c.
†Antisheep	119	79	95	100
†Antiox	50	46	78	90
††Antiguinea pig	57	81	98	98
†Antidog	25	93	98	100
††Antirabbit	50	78	98	98
††Antirat*	25	4	40	76
†Antichick	36	4	62	77
†Antihog (swine)	50	46	82	90
††Antihuman	78	0	4	9

† = Corpuscles of one animal used.

†† = Mixed corpuscles from six animals employed.

* *Mus norvegicus* (var. *albinus*).

TABLE IV

THERMOLABILE HEMOLYSINS IN HUMAN SERA FOR THE ERYTHROCYTES OF DIFFERENT RATS*

SERUM NO.	RESULTS WITH VARIOUS ERYTHROCYTE SUSPENSION					
	Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6
1	—**	+	—	—	—	—
2	—	—	—	+	+	—
3	—	—	—	—	—	—
4	—	+	+	+	—	—
5	—	—	—	—	—	—
6	—	—	—	—	—	—
7	—	—	—	—	—	+
8	—	—	—	—	—	+
9	—	—	—	—	—	—
10	—	—	+	+	+	—
11	—	—	—	—	—	—
12	+	+	+	+	—	+
13	—	—	—	—	—	—
14	—	+	+	+	—	—
15	—	—	—	—	—	—
16	—	—	—	—	—	—
17	—	—	—	—	—	—
18	—	+	—	—	—	—
19	—	—	—	+	—	—
20	—	—	+	—	—	—
21	—	—	—	—	—	—
22	—	—	+	+	—	+
23	—	—	—	—	—	—
24	—	+	+	+	+	+
25	—	—	+	—	—	+

* *Mus norvegicus* (var. *albinus*)

** — = no hemolysis; + = hemolysis

groups of hemolysins for the erythrocytes of each of the various lower animals as has been done by Moss, Ottenburg and others for the isohemolysins in human sera.

Results.—Table III gives a summary of the results using single and multiple suspensions of the erythrocytes of various animals;

TABLE V

THERMOLABILE HEMOLYSINS IN HUMAN SERA FOR THE ERYTHROCYTES OF VARIOUS GUINEA PIGS

SERUM* NO.	RESULTS WITH VARIOUS SUSPENSIONS					
	1	2	3	4	5	6
1	+	+	+	+	+	+
2	+	—	—	+	+	+
3	+	+	+	+	+	+
4	+	+	—	+	+	+
5	+	+	+	+	+	+
6	+	+	—	+	+	—
7	+	+	+	+	+	+
8	+	+	+	+	+	+
9	+	+	+	+	+	+
10	+	+	+	+	—	+
11	+	+	+	+	+	+
12	+	+	+	+	—	+
13	+	+	+	+	—	+
14	+	+	+	+	+	+
15	+	+	+	+	+	+
16	+	+	+	+	+	+
17	+	+	+	+	+	+
18	+	+	+	+	—	+
19	+	+	+	+	+	+
20	+	—	+	+	—	—

*sera used in dose of 0.1 c.c.

** + = agglutination; — = no agglutination.

TABLE VI

SHOWING PERCENTAGE OF HUMAN SERA IN AMOUNTS OF 0.1 C.C. CONTAINING THERMOLABILE HEMOLYSINS FOR THE ERYTHROCYTES OF DIFFERENT ANIMALS OF THE SAME SPECIES

ERYTHRO- CYTES	PERCENTAGE OF SERA SHOWING THE PRESENCE OF HEMOLYSIN FOR THE CORPUSCLES OF SIX DIFFERENT SUSPENSIONS					
	Suspension 1	Suspension 2	Suspension 3	Suspension 4	Suspension 5	Suspension 6
Sheep	90%	90%	95%	85%	95%	95%
Ox	72%	81%	81%	81%	81%	88%
Guinea pig	100%	90%	90%	100%	98%	92%
Rabbit	100%	94%	100%	96%	100%	100%
Rat	4%	24%	32%	32%	12%	28%
Hog	100%	90%	96%	100%	92%	92%
Human	0	4%	44%	44%	40%	0

Tables IV and V show the grouping of thermolabile hemolysins in human sera for guinea pig and rat erythrocytes, the results of similar tests with sheep and human erythrocytes having been given in the paper on complements previously referred to.¹ Table VI gives a summary of the results of tests for group thermolabile hemolysins in human sera for the corpuscles of various animals.

As shown in Table III, human sera are remarkably rich in thermolabile hemolysins for a variety of animals and especially when tested in amounts of 0.2 c.c. These hemolysins show grouping as is true of the thermolabile hemolysins in human sera for human corpuscles; with such hemolysins as those for sheep and guinea pig cells, the presence of groups is not as evident as for the cells of persons and rats, because the majority of human sera contain varying amounts of these thermolabile hemolysins (Table VI).

THERMOSTABLE HEMOLYSINS IN HUMAN SERUM

Technic.—The majority of tests for these hemolysins were conducted with the same sera employed in the tests for thermolabile hemolysins after being heated in a water-bath at 56° C. for thirty minutes and used in doses of 0.05, 0.1 and 0.2 c.c. with 0.1 c.c. of 5 per cent suspensions of washed corpuscles. Complement was furnished in dose of 0.1 c.c. of 1:10 dilutions of the mixed sera of guinea pigs previously absorbed at a low temperature with the

TABLE VII

PERCENTAGE OF HUMAN SERA IN VARYING AMOUNTS CONTAINING THERMOSTABLE HEMOLYSINS FOR THE ERYTHROCYTES OF VARIOUS ANIMALS

HEMOLYSINS	SERA TESTED	PERCENTAGE OF SERA SHOWING PRESENCE OF HEMOLYSINS		
		0.05 c.c.	0.1 c.c.	0.2 c.c.
†Antisheep	119	76	72	89
††Antirabbit	50	57	60	63
†Antihog (swine)	50	45	60	60
†Antiox	50	45	47	47
††Antiguinea pig	57	0	5	5
†Antidog	25	0	4	4
††Antirat*	25	0	4	4
†Antichicken	36	0	0	2
††Antihuman	78	0	0	0

†Corpuscles of one animal used.

††Mixed corpuscles from six animals employed.

*Mus Norvegicus (var. albinus).

TABLE VIII
THERMOSTABLE HEMOLYSINS IN HUMAN SERA FOR THE ERYTHROCYTES OF
VARIOUS PERSONS

SERUM* NO.	RESULTS WITH VARIOUS SUSPENSIONS					
	1	2	3	4	5	6
1	—**	—	—	—	—	—
2	—	—	—	—	—	—
3	—	—	—	—	—	—
4	—	—	—	—	—	—
5	—	+	—	—	—	—
6	—	—	—	—	—	—
7	—	—	—	—	—	—
8	—	—	—	—	—	—
9	—	—	—	—	—	—
10	—	—	—	—	—	—
11	—	—	—	—	—	—
12	—	—	—	—	—	—
13	—	—	—	—	—	—
14	—	—	—	—	—	—
15	—	—	—	—	—	—
16	—	—	—	—	—	—
17	—	—	—	—	—	—
18	—	—	—	—	—	—
19	—	—	—	—	—	—
20	—	—	—	—	—	—

** — = no hemolysis; + = hemolysis.

*Sera used in dose of 0.1 c.c.

TABLE IX
THERMOSTABLE HEMOLYSINS IN HUMAN SERA FOR THE ERYTHROCYTES OF
VARIOUS SHEEP

SERUM* NO.	RESULTS WITH VARIOUS SUSPENSIONS					
	1	2	3	4	5	6
1	—**	+	+	+	+	+
2	+	+	+	+	+	+
3	+	—	—	—	—	—
4	—	—	—	—	—	—
5	+	+	+	+	+	+
6	+	+	+	+	+	+
7	+	+	+	+	+	+
8	+	+	+	+	+	+
9	+	+	+	+	+	+
10	+	+	+	+	+	+
11	+	+	+	+	+	+
12	+	+	+	+	+	+
13	+	+	+	+	+	+
14	+	+	+	+	+	+
15	—	—	—	—	—	—
16	—	—	—	—	—	—
17	+	+	+	+	+	+
18	+	+	+	+	+	+
19	+	+	+	+	+	+
20	+	+	+	+	+	+

*Sera used in dose of 0.1 c.c.

**+ = agglutination; — = no agglutination.

TABLE X
THERMOSTABLE HEMOLYSINS IN HUMAN SERA FOR THE ERYTHROCYTES OF
VARIOUS GUINEA PIGS

SERA* NO.	RESULTS WITH VARIOUS SUSPENSIONS					
	1	2	3	4	5	6
1	—**	—	—	—	—	—
2	—	—	—	—	—	—
3	—	—	—	—	—	—
4	—	—	—	—	—	—
5	+	+	+	+	+	+
6	—	—	—	—	—	—
7	+	+	+	+	+	+
8	+	+	+	+	+	+
9	+	+	—	—	+	+
10	—	—	—	—	—	—
11	—	—	—	—	—	—
12	—	—	—	—	—	—
13	+	+	+	+	+	+
14	—	—	—	—	—	—
15	—	—	—	—	—	—
16	—	—	—	—	—	—
17	—	—	—	—	—	—
18	—	—	—	—	—	—
19	—	—	—	—	—	—
20	—	—	—	—	—	—

*Sera used in dose of 0.1 c.c.

**— = no agglutination; + = agglutination.

TABLE XI
PERCENTAGE OF HUMAN SERA IN AMOUNTS OF 0.1 C.C. CONTAINING THERMOSTABLE
HEMOLYSINS FOR THE ERYTHROCYTES OF DIFFERENT ANIMALS OF THE SAME
SPECIES

ERYTHRO- CYTES	PERCENTAGE OF SERA SHOWING THE PRESENCE OF HEMOLYSIN FOR THE CORPUSCLES OF SIX DIFFERENT SUSPENSIONS					
	Susp. 1	Susp. 2	Susp. 3	Susp. 4	Susp. 5	Susp. 6
Human	0	0	0	4%	0	0
Sheep	90%	90%	90%	80%	80%	95%
Ox	10%	15%	10%	5%	15%	30%
Guinea pig	25%	25%	20%	20%	25%	25%
Rabbit	2%	0	0	0	0	0
Hog	2%	0	4%	0	15%	0
Rat	2%	0	0	2%	0	0

corpuscles under study, in order to remove the natural hemolysin. Saline solution was added to bring the total volume to 1.5 c.c. and incubation conducted in a water-bath at 38° C. for one hour, the readings being made after the tubes had stood in a refrigerator overnight. In each experiment controls on the presence of natural

hemolysin in the complement serum were included and always showed absolute removal by the process of absorption.

Results.—Table VII gives a summary of the results using single and multiple suspensions of the erythrocytes of various animals; Tables VIII, IX, and X show the grouping of these thermostable hemolysins for the corpuscles of persons, sheep, and guinea pigs, a summary of these group hemolysins being given in Table XI.

The results of these studies have proved very interesting and may be summarized as follows:

1. Thermostable antisheep hemolysin is most commonly present in human sera while antihuman hemolysin is least commonly present (Table VII).

2. Thermostable hemolysins do not show the tendency for grouping to even nearly the same extent as shown by the thermolabile hemolysins.

3. The isohemolysins in human sera are practically entirely of the thermolabile variety. The majority are inactivated at 56° C. for one-half hour and all by heating at 62° C.

4. From the standpoint of choice of corpuscles for the indicator antigen in the Wassermann test human, chicken, guinea pig and rat cells are all better adapted than sheep cells, insofar as these thermostable hemolysins are concerned; other factors, however, as the presence of agglutinins and the ease or difficulty of production of immune hemolysin by the immunization of rabbits, must be taken into consideration.

These results agree fairly closely with those reported by Kolmer and Casselman⁶ on the presence of natural hemolysins in heated human sera for the corpuscles of a variety of animals, and the differences are probably due to the group hemolysins inasmuch as their work was conducted with the corpuscles of a single animal of each species.

The amount of any particular hemolysin in a unit of serum depends, of course, upon the amount of complement and corpuscle suspension employed in the tests; as stated above antisheep hemolysin is most commonly present in heated sera and quantitative tests indicate that it is usually present in the largest amount. In tests of this character with twenty-eight sera used in doses varying from 0.01 to 0.2 c.c. with 0.1 c.c. of hemolysin-free guinea pig complement diluted 1:10 and 0.1 c.c. of a 5 per cent suspension of cells

from one sheep, complete hemolysis was produced by two sera in dose of 0.01 c.c., by six sera in dose of 0.02 c.c. and the remaining twenty sera in doses varying from 0.04 to 0.2 c.c.

THE RELATION BETWEEN THERMOLABILE AND THERMOSTABLE
HEMOLYSINS IN HUMAN SERUM

In every instance the average hemolytic activity of unheated human serum for the erythrocytes of various animals was higher than heated sera; indeed the hemolysins for human, guinea pig, rabbit, hog and rat erythrocytes are almost entirely of the thermolabile variety. Part of this difference may be due to the fact that human complement activates certain of these natural hemolytic amboceptors better than guinea pig complement and that the reduction in hemolytic activity in heated serum is due to the destruction of native complement rather than of thermolabile hemolysin. Special studies bearing upon this subject indicate that the differences are largely due to destruction of hemolysins by heat rather than to the destruction of complement;⁵ but whatever the true explanation may be, the fact remains that fresh unheated serum is more hemolytic than heated serum and that this influences the question of using heated or unheated serum and the choice of an indicator antigen for a standardized Wassermann test.

The results of comparative tests with the same sera before and after heating and the erythrocytes of different animals are shown in Tables III and VII indicating the marked reduction in the hemolytic activity of heated sera tested in graded amounts.

Table XII gives a summary of the thermolabile and thermostabile hemolysins in human sera on the basis of testing each serum with suspensions of corpuscles from at least six different animals of each species; the presence of group hemolysins is brought out quite clearly and especially in the unheated sera. Thermolabile hemolysins for human cells were found in 4 to 44 per cent of sera as tested with six different suspensions chosen at random and the percentages for the corpuscles of certain of the lower animals are shown as observed with a similar technic.

Striking differences in the hemolytic activity of active and heated sera were observed with the corpuscles of the rabbit, hog, guinea pig and ox; as shown in this table the hemolysins for these cor-

puscles are very largely of the thermolabile variety; curiously enough the hemolysin for sheep cells was found most resistant of those studied, the differences between the hemolytic activity of active and heated serum being very slight.

TABLE XII

SHOWING PERCENTAGE OF THERMOLABILE AND THERMOSTABILE HEMOLYSINS IN HUMAN SERA

ERYTHROCYTES	THERMOLABILE	THERMOSTABILE
Human	4 to 44%	0 to 4%
Sheep	85 to 95%	80 to 95%
Ox	72 to 88%	5 to 30%
Guinea pig	90 to 100%	20 to 25%
Rabbit	94 to 100%	0 to 2%
Hog	92 to 100%	0 to 15%
Rat	4 to 32%	0 to 2%

Part 2

THERMOLABILE AND THERMOSTABILE HEMAGGLUTININS IN HUMAN SERA

From the standpoint of the complement-fixation reaction the presence of hemagglutinins in the serum being tested may be a matter of importance, and particularly in the antihuman hemolytic system; agglutination of the corpuscles delays or interferes with hemolysis and not infrequently renders the end results unsatisfactory. With the antihuman system these agglutinins may be in the rabbit immune hemolysin, the patient's serum or both; the phenomenon is practically never encountered with the antisheep and antiox hemolytic systems because of the usual highly potent nature of the rabbit immune hemolysins and the infrequency of agglutinins for sheep and ox corpuscles in human sera.

Agglutinins are generally regarded as resistant to heat, desiccation and other deleterious influences; it is highly probable, however, that some of the natural hemagglutinins in human sera are thermolabile although not quite as susceptible to heat as the hemolysins. The subject is of interest and some importance in relation to the use of heated or unheated serum in the conduct of complement-fixation tests.

In our experiments heating sera at 56° C. for thirty minutes usually removed a portion of the natural hemagglutinins; heating at 62° C. for the same period of time invariably removed all of these agglutinins. Since sera are heated at 56° C. for the Wassermann test, we

have adopted this degree of heat for differentiating thermolabile and thermostabile hemagglutinins, although in our experience all of these agglutinins are destroyed at 62° C. and in this sense are thermolabile, whereas immune hemagglutinins produced by injecting rabbits with alien erythrocytes are not totally removed by this degree of heat, although some deterioration occurs.

The Influence of Heat upon Natural Hemagglutinins.—The influence of heat upon agglutinins for human erythrocytes in human sera, is shown in Tables XIII and XIV; as shown in Table XIII, the majority of these agglutinins do not tend to deteriorate until the sera have been heated to 58°-60° C. for at least thirty minutes. Deterioration is more marked at 60° C. and completed at 62° C. As shown in Table XIV deterioration may begin in five minutes at 62° C. and is always well marked after fifteen minutes and complete after twenty to thirty minutes.

TABLE XIII

THE INFLUENCE OF HEAT UPON ISOHEMAGGLUTININS IN HUMAN SERA

SERA	ACTIVE SERA	EFFECT OF HEATING FOR 30 MINUTES				
		50°C.	56°C.	58°C.	60°C.	62°C.
19	+	+	—	—	—	—
32	+	+	+	+	—	—
53	+	+	+	+	—	—
74	+	+	+	+	±	—

*+= agglutination; ±=partial agglutination; —= no agglutination.

TABLE XIV

THE INFLUENCE OF HEATING HUMAN SERA AT 62° UPON ISOHEMAGGLUTININS

SERA	ACTIVE SERA	EFFECT OF HEATING					
		5 min.	10 min.	15 min.	20 min.	25 min.	30 min.
19	+	—	—	—	—	—	—
32	+	+	+	—	—	—	—
53	+	+	—	—	—	—	—
74	+	+	+	+	+	±	—

*+= agglutination; ±= partial agglutination; —= no agglutination.

THERMOLABILE HEMAGGLUTININS

A study of hemagglutinins in fresh unheated sera is complicated by the occurrence of partial or complete hemolysis; this is particularly true in tests for agglutinins for such erythrocytes as those of sheep and guinea pig because over 90 per cent of human sera con-

tain hemolysins for these cells. The only avenue of approach was the use of sera inactivated by aging in a refrigerator or at room temperature, although it is probable that agglutinin may deteriorate under these conditions as well as complement.

Technic.—Tests for thermolabile hemagglutinins were conducted by placing 0.05 or 0.1 c.c. of each serum fresh and unheated or aged and unheated, in a series of six small test tubes and adding 1 c.c. of 1 per cent suspensions of the washed erythrocytes from six different animals of each species studied taken more or less at random; these mixtures and the controls were placed in a water-bath at 38° C. and the readings made after standing in a refrigerator overnight. It should be emphasized that all tests were conducted with this macroscopic technic, inasmuch as a microscopic technic is probably more delicate in the detection of agglutination and may have yielded a higher percentage of positive reactions than observed in our experiments.

Results.—A summary of the results of agglutination tests conducted with unheated human sera and six different suspensions of the erythrocytes of persons, rats, rabbits, oxen, and sheep, is shown in Table XV; the presence of group agglutinins for the corpuscles of the lower animals as well as of persons, is shown in this table inasmuch as the results varied with suspensions from different animals of each species studied.

TABLE XV

SHOWING THE PERCENTAGE OF UNHEATED HUMAN SERA IN DOSE OF 0.1 C.C. CONTAINING AGGLUTININS FOR THE ERYTHROCYTES OF DIFFERENT ANIMALS OF THE SAME SPECIES

ERYTHROCYTES	RESULTS WITH THE CORPUSCLES OF SIX DIFFERENT SUSPENSIONS					
	Suspension 1	Suspension 2	Suspension 3	Suspension 4	Suspension 5	Suspension 6
Sheep	20	0	0	4	4	16
Ox	16	25	8	16	0	0
Rabbit	80	70	60	90	44	44
Rat	15	20	15	25	20	40
Human	45	0	0	30	65	20

These percentages, however, are misleading, inasmuch as the number of positive reactions were frequently lower than observed with the same sera after heating at 56° C. for thirty minutes, due partly to the influence of hemolysins in the active sera producing slight

or well marked hemolysis and rendering the interpretation of the agglutination tests difficult and uncertain.

The influence of heating sera at 56° C. for thirty minutes on natural hemagglutinins is better shown in Tables XVI, XVII, and XVIII; slight deterioration generally occurred, but in an irregular manner, that is, hemagglutinins for certain corpuscles were destroyed while others were not. The presence of group agglutinins in human sera for the corpuscles of the lower animals is also shown in these tables.

THERMOSTABLE HAMAGGLUTININS

Technic.—These tests were conducted in the same manner as described except that the sera were first heated on a water-bath at 56° C. for thirty minutes. In certain experiments duplicate tests were set up at the same time with portions of the same sera heated at 62° C.

Results.—The influence of heating sera at 56° C. is best shown in Tables XVI, XVII, and XVIII; in every instance the natural hemagglutinins are completely destroyed by heating at 62° C. and in this sense none of the natural or normal hemagglutinins is ther-

TABLE XVI

THE INFLUENCE OF HEAT UPON NATURAL ISOHEMAGGLUTININS IN HUMAN SERA *

SERUM	ACTIVE SERA						SERA HEATED AT 56° C.						SERA HEATED AT 62° C.					
	I**	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
1	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-
13	+	-	-	-	+	-	+	-	-	-	+	-	-	-	-	-	-	-
24	+	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-
29	+	+	-	+	+	+	+	-	-	+	-	+	-	-	-	-	-	-
32	+	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-	-
29	-	-	-	+	-	+	+	-	-	-	-	+	-	-	-	-	-	-
30	+	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
32	+	-	+	+	-	-	+	-	+	+	-	-	-	-	-	-	-	-
35	+	-	+	+	-	-	+	-	+	+	-	-	-	-	-	-	-	-
44	+	-	+	+	-	-	+	-	+	+	-	-	-	-	-	-	-	-
47	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-
59	+	-	+	+	-	-	+	-	+	+	-	-	-	-	-	-	-	-

* Used in dose of 0.05 c.c. with sera Nos. 1, 13, 24, 28, 32 and 29; in dose of 0.1 c.c. with sera 30, 32, 35, 44, 47 and 49.

** Suspensions of erythrocytes from six different persons chosen at random.

mostabile. Immune hemagglutinins, as those produced by injecting rabbits with human erythrocytes, are more resistant and suffer only partial deterioration at this temperature.

The presence of group agglutinins in heated sera for guinea-pig erythrocytes is shown in Table XIX; similar results observed with human and sheep cells have been given in a previous communication.¹ A summary of these experiments is given in Table XX which shows

TABLE XVII
THE INFLUENCE OF HEAT UPON NATURAL AGGLUTININS FOR RABBIT ERYTHROCYTES IN HUMAN SERA *

SERA	ACTIVE SERA						SERA HEATED AT 56° C.						SERA HEATED AT 62° C.					
	1**	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
1	+	+	+	+	-	-	+	-	-	-	-	+	-	-	-	-	-	-
2	+	+	+	+	+	+	+	+	+	-	+	+	-	-	-	-	-	-
3	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-
4	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-
6	+	+	-	-	+	+	+	+	-	-	+	-	-	-	-	-	-	-
7	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-

* Use in dose of 0.05 c.c.
** Suspensions of erythrocytes from six different rabbits chosen at random.

TABLE XVIII
THE INFLUENCE OF HEAT UPON NATURAL AGGLUTININS FOR RAT ERYTHROCYTES IN HUMAN SERA.*

SERA	ACTIVE SERA						SERA HEATED AT 56° C.						SERA HEATED AT 62° C.					
	1**	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
3	-	+	-	+	+	+	-	+	-	+	+	+	-	-	-	-	-	-
19	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-
15	-	+	+	+	+	+	-	+	+	+	+	+	-	-	-	-	-	-
16	+	+	-	+	-	-	+	+	-	-	-	-	-	-	-	-	-	-
20	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-
24	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-

* Use in dose of 0.1 c.c.
** Suspensions of erythrocytes from six different rats (mus norvegicus var. albinus) chosen at random.

the percentages of positive reactions with suspensions of erythrocytes from six different animals of the same species and the futility of expressing results of such experiments conducted with the corpuscles of any one animal of a given species. Table 21 shows the results of tests conducted with a compound or mixed suspension of the erythrocytes of persons and certain of the lower animals prepared by mixing equal parts of the washed cells from six different animals of each species into one antigen; these mixed antigens are more likely to yield true results than tests conducted with the cells of one person or lower animal.

RELATION BETWEEN THERMOLABILE AND THERMOSTABLE
HEMAGGLUTININS

While heating sera at 56° C. for thirty minutes tends to destroy or reduce the natural hemagglutinins to some extent, not infrequently

TABLE XIX
AGGLUTININS IN HEATED HUMAN SERA FOR THE ERYTHROCYTES OF VARIOUS
GUINEA PIGS

SERUM* NO.	RESULTS WITH VARIOUS SUSPENSIONS					
	1	2	3	4	5	6
1	++	—	+	+	+	—
2	+	+	+	+	+	—
3	+	—	+	+	+	+
4	—	—	—	—	—	—
5	—	—	—	—	—	—
6	—	—	—	—	—	—
7	—	—	—	—	+	—
8	—	—	—	—	—	—
9	—	—	—	—	—	—
10	+	+	+	+	+	+
11	—	—	—	—	—	—
12	—	—	—	—	—	—
13	—	—	—	—	—	—
14	—	—	—	—	—	—
15	—	—	—	—	—	—
16	—	—	—	—	—	—
17	+	—	—	—	—	—
18	—	—	—	—	—	—
19	—	—	—	—	—	—
20	+	+	+	+	+	+
21	—	—	—	—	+	—
22	—	—	—	—	—	—
23	+	+	+	+	+	+
24	+	+	+	+	+	+
25	—	—	—	—	—	—

*sera used in dose of 0.1 c.c.

**+ = agglutination; — = no agglutination.

TABLE XX

SHOWING PERCENTAGE OF HEATED HUMAN SERA IN DOSE OF 0.2 C.C. CONTAINING
AGGLUTININS FOR THE ERYTHROCYTES OF DIFFERENT ANIMALS OF THE
SAME SPECIES

ERYTHROCYTES	RESULTS WITH THE CORPUSCLES OF SIX DIFFERENT SUSPENSIONS					
	Suspension 1	Suspension 2	Suspension 3	Suspension 4	Suspension 5	Suspension 6
Sheep	36%	20%	12%	24%	12%	4%
Ox	16%	4%	0%	0%	40%	12%
Guinea Pig	32%	20%	28%	28%	36%	24%
Rabbit	90%	100%	100%	100%	90%	100%
Rat	70%	70%	78%	66%	68%	85%
Hog	90%	84%	90%	90%	64%	84%
Human	52%	4%	52%	80%	56%	48%

TABLE XXI

PERCENTAGE OF HEATED HUMAN SERA IN DOSE OF 0.2 C.C. CONTAINING NATURAL
AGGLUTININS FOR MIXTURE OF THE CORPUSCLES OF SEVERAL ANIMALS
OF VARIOUS SPECIES

ERYTHROCYTES	TOTAL SERA EXAMINED	NUMBER POSITIVE	PERCENTAGE POSITIVE REACTIONS
Sheep	24	4	20
Ox	48	2	4
Guinea Pig	43	14	32
Rabbit	49	47	95
Rat	25	10	40
Hog	49	38	77
Dog	25	22	88
Chicken	25	1	4
Human	49	23	47

a hemolysin-free and active serum produces no agglutination whereas the same serum after heating does produce agglutination of the same corpuscles. As a general rule the percentages of positive reactions is greater with heated than with active sera, as shown in Table XXII; this is partly due to the fact that active sera may produce partial hemolysis and thereby reduce the percentage of positive agglutination reactions; but this is not the whole explanation, inasmuch as we have occasionally observed that hemolysin-free sera may produce agglutination only after being heated at 56° C. for thirty minutes.

THE RELATION BETWEEN NATURAL HEMOLYSINS AND HEMAGGLUTININS
IN HUMAN SERA

The relation between the presence of natural isohemolysins and hemagglutinins in human sera has always been an interesting subject in relation to the transfusion of blood; many serologists believe that tests for hemagglutinins are sufficient, and if found absent, that one may assume that hemolysins are likewise absent.

With the *macroscopic technic* employed in this investigation we have frequently found that hemolysins may be present for certain corpuscles and hemagglutinins absent or, as occurs more frequently the reverse may be observed; this was found not only with the hemolysins and hemagglutinins for human erythrocytes, but more especially for the cells of some of the lower animals. For example, thermolabile and thermostabile hemolysins for sheep corpuscles were found in at least 90 per cent of human sera, while hemagglutinins were found in only 4 to 36 per cent; on the other hand hemolysins for rat corpuscles were found in 4 to 32 per cent of active sera, whereas hemagglutinins were present in 65 to 85 per cent of the same sera (Table XXII).

TABLE XXII

SUMMARY SHOWING PERCENTAGE OF HUMAN SERA CONTAINING HEMOLYSINS AND AGGLUTININS FOR THE ERYTHROCYTES OF VARIOUS ANIMALS

ERYTHROCYTES	HEMOLYSINS		AGGLUTININS	
	THERMOLABILE	THERMOSTABILE	THERMOLABILE	THERMOSTABILE
Human	4 to 44	0 to 4	20 to 65	4 to 80
Sheep	85 to 95	80 to 95	4 to 20	4 to 36
Ox	72 to 88	5 to 30	0 to 30	4 to 40
Guinea Pig	90 to 100	20 to 25	—	24 to 36
Rabbit	94 to 100	0 to 2	80 to 100	90 to 100
Rat	4 to 32	0 to 2	15 to 40	66 to 85
Hog	92 to 100	0 to 15	—	64 to 90
Dog	about 98	about 4	—	about 88
Chicken	about 62	0	—	0 to 4

It is evident, therefore, that a hemolysin for particular corpuscles may be present in a fresh unheated serum and agglutinin absent; with the isohemolysins and hemagglutinins in human sera this is seldom found, but nevertheless may occur and questions the practice of basing an opinion upon the suitability of a blood for transfusion on the basis of agglutination tests alone. In Tables XXIII

and XXIV are shown the results of tests employing fresh unheated human sera in amounts of 0.2 c.c. with 1 c.c. of 1 per cent suspensions of washed corpuscles from six different persons and rats taken at random. Isohemagglutinins were found in a higher percentage of sera than isohemolysins, but occasionally a hemolysin was present for certain corpuscles when agglutinins were absent according to the *results of a macroscopic technic* (Sera 2 and 3, Table XXIII); similar tests employing corpuscles from six different rats showed quite conclusively that hemolysin for certain cells may be present and agglutinin absent or the reverse (Table XXIV).

TABLE XXIII

THE RELATION OF ISOHEMOLYSINS AND ISOHEMAGGLUTINATION IN ACTIVE HUMAN SERA

SERA	EFFECT UPON CORPUSCLES FROM DIFFERENT PERSONS					
	CORP. 1	CORP. 2	CORP. 3	CORP. 4	CORP. 5	CORP. 6
1	N-*	H+	H+	N+	H+	N-
2	H-	H+	H+	H+	H+	N-
3	N-	N-	H-	N-	H-	N-
4	N-	H+	H+	N-	H+	N-
5	N-	N+	N+	N+	N+	N+
6	N-	N-	N-	H+	N-	N-
7	N-	H+	H+	N-	H+	N-
8	N-	N-	N-	N+	N-	N-
9	N-	N-	N-	N+	N-	N-
10	N-	N+	N-	N-	N-	N-

*N=no hemolysis; H=hemolysis; --no agglutination; +=agglutination.

TABLE XXIV

RELATION BETWEEN THE HEMOLYSINS AND HEMAGGLUTININS IN ACTIVE HUMAN SERA FOR RAT CORPUSCLES

SERA	EFFECT UPON CORPUSCLES FROM SIX DIFFERENT RATS					
	CORP. 1	CORP. 2	CORP. 3	CORP. 4	CORP. 5	CORP. 6
1	H+*	H+	H+	H+	H+	H+
2	N+	N+	N+	N+	N+	N+
3	H-	H-	H-	H-	H-	H-
4	N+	N+	N+	N+	H-	N-
5	H-	H-	H+	N+	H-	N-
6	N+	N+	N+	N+	N+	N+
7	H-	H-	H+	H+	H+	H+
8	H+	H-	H+	H+	H+	H+
9	H-	H+	H+	H-	H-	H-
10	N-	N-	N+	N-	N-	N-

*H=hemolysis; N=no hemolysis; +=agglutination; --no agglutination.

DISCUSSION

As shown in the summary of natural thermolabile and thermostable hemolysins and hemagglutinins in human sera presented in Table XXII, the choice of erythrocytes for a hemolytic system for a standardized technic based upon the absence of these substances from human sera, depends to a large extent upon whether active or heated sera are employed; active human sera contain hemolysins for such a wide variety of animals that the choice should be undoubtedly human erythrocytes because isohemolysins are present in a smaller percentage of sera and where present the amount contained in 0.1 or 0.2 c.c. of serum is seldom large. Rat erythrocytes would be second choice on this basis, but owing to the small amount of blood obtainable from these animals, an antirat hemolytic system is not feasible.

With heated human sera the choice of corpuscles for the hemolytic system is wider because the process of heating removes much of the various natural hemolysins, but the question of the presence of hemagglutinins becomes more important inasmuch as heated sera are usually more agglutinative than unheated; chicken or human erythrocytes appear to be most suitable. The natural hemolysins for rabbit, rat, dog, and hog erythrocytes are largely removed by heating the sera, but agglutinins for these cells are present in prominent degree. Although the antisheep hemolytic system is so widely employed, it is the least desirable judged on the basis of the presence of natural hemolysin and far inferior in this respect to an antiox system.

Since the presence of a natural hemolysin for the corpuscles of the indicator antigen in the complement serum or person's serum being tested, tends to disturb quantitative relations in the hemolytic system and thereby reduce the delicacy of the complement-fixation reaction, these natural hemolysins have attracted most attention; the hemagglutinins have scarcely been considered at all in this connection. The reason is apparent, inasmuch as most attention has been devoted to the presence and influence of natural antisheep hemolysin in human sera and hemagglutination is scarcely if ever in evidence because hemagglutinins for sheep cells are present in but a small percentage of sera and their influence readily overcome by powerful immune hemolysins which are so easily prepared in rab-

bits; the same is true of the antioxy system. But when an anti-human hemolytic system is employed, the role played by hemagglutinins is more important inasmuch as the human sera being tested may contain hemagglutinin for the corpuscles of the indicator antigen as well as the rabbit immune hemolysin; the only practical method for overcoming the retarding effect of hemagglutination upon hemolysis is the employment of powerful rabbit immune hemolysins, unless the sera are absorbed by the corpuscles used in making up the indicator antigen prior to being used in the complement-fixation tests, which is too laborious and time-consuming for routine work.

Therefore a final decision regarding the corpuscles best suited for a hemolytic system for the conduct of complement-fixation tests with the human sera, is influenced by the ease or difficulty with which blood is obtainable and rabbit immune hemolysins prepared; also the actual rather than the theoretic influence exerted upon the delicacy of the Wassermann test by the natural hemolysins and hemagglutinins in human sera. Both of these subjects have received a special study and the results are given elsewhere. (2,7)

SUMMARY

1. The natural hemolysins and hemagglutinins in human sera may be divided into two varieties, namely, the *thermolabile hemolysins and hemagglutinins*, those destroyed by heating the sera at 56° C. for thirty minutes and the *thermostabile hemolysins and hemagglutinins*, those which withstand this exposure.

2. All natural hemolysins and hemagglutinins in human sera with the occasional exception of antisheep hemolysin, are destroyed or inactivated by heating the sera at 62° C. for thirty minutes; immune hemolysins and hemagglutinins, as those produced by injecting rabbits with human cells, are generally more resistant and suffer only partial deterioration with this exposure.

3. The thermolabile hemolysins and hemagglutinins in human sera for the erythrocytes of the lower animals are present in groups analogous to the groups of the isohemolysins and isohemagglutinins in human sera; for this reason percentages expressing the presence of natural hemolysins and hemagglutinins based upon studies made with the corpuscles of a single animal of each species are only approximately correct.

4. Heating human sera at 56° C. for thirty minutes largely removes the group hemolysins and to a lesser extent the hemagglutinins; thermostabile hemolysins and hemagglutinins do not show the same tendency for grouping.

5. A large percentage of fresh human sera contain a variety of hemolysins for erythrocytes of the lower animals; least is present for human cells, but for the cells of the sheep, ox, guinea pig, dog, rabbit, rat, chicken and hog, thermolabile hemolysins are present in from 40 to 100 per cent of sera.

6. Natural hemolysins in human sera for the erythrocytes of persons, rabbits, hogs, guinea-pigs and oxen, are very largely of the thermolabile variety.

7. Heated human sera contain lesser amounts of natural hemolysins; that for sheep erythrocytes is most commonly present, being found in 80 to 95 per cent of sera; antiox hemolysin was found in 5 to 30 per cent, antiginea pig hemolysin in 20 to 25 per cent and antihuman, antirabbit, antihog, and antirat hemolysins in 0 to 15 per cent of sera.

8. Natural hemagglutinins in human sera are more resistant to heat than the natural hemolysins.

9. Although heating sera at 56° C. tends to destroy some of the natural hemagglutinins, yet heated sera yield a higher percentage of positive agglutination reactions than unheated sera due in part to the influence of hemolysins in the latter.

10. Thermostabile hemagglutinins were present in about 95 per cent of human sera; named in the order of highest percentage present were the hemagglutinins for the erythrocytes of dogs, hogs, persons, rats, guinea pigs, sheep, and chickens.

11. There is no relation between the occurrence of hemolysins and hemagglutinins in heated human sera. For example, 90 per cent of sera contain agglutinins for rabbit erythrocytes and less than 2 per cent contain hemolysins for the same corpuscles; from 4 to 80 per cent of sera contain agglutinins for human cells and 0 to 4 per cent contain hemolysins. For sheep erythrocytes, however, conditions are reversed inasmuch as 80 to 95 per cent of heated sera contain hemolysins for these cells and only 4 to 36 per cent contain hemagglutinins. There is likewise no relation between the occurrence of hemolysins and hemagglutinins in active sera; hemagglutinins for the corpuscles of certain animals of a species may

be present and hemolysins absent or the reverse may be observed.

12. In reference to the Wassermann and other complement-fixation tests the presence of natural hemolysins and hemagglutinins in human sera are important in relation to the hemolytic system; theoretically at least the presence of a natural hemolysin for the corpuscles of the indicator antigen tends to disturb quantitative conditions in the hemolytic system and reduce the delicacy of the complement-fixation test, while an agglutinin may interfere with hemolysis particularly with a low titre rabbit immune hemolysin and thereby interfere with the sharpness of the reactions. Judged solely on this basis human corpuscles are best adapted for complement-fixation tests employing active or unheated human sera; with inactivated or heated sera, human or chicken corpuscles are best suited. Other factors, however, are to be considered before a decision can be made on the best hemolytic system for a standardized technic, namely, the actual rather than theoretic influence of natural hemolysins and hemagglutinins and practical means for overcoming their influence, the ease or difficulty by which blood is obtainable and more particularly, by the ease or difficulty by which immune hemolysins are prepared by injecting the corpuscles of persons and various of the lower animals into rabbits.

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STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION.* VIII

THE INFLUENCE OF NATURAL ANTISHEEP HEMOLYSIN IN HUMAN SERA UPON THE WASSERMANN REACTION

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THE presence of natural antisheep hemolysin in human sera and its influence upon the results of complement-fixation tests in syphilis, has been the subject of numerous investigations with conflicting results and opinions; those who employ an antihuman hemolytic system appear convinced that the reactions are more sensitive owing to the absence of these natural hemolysins while numerous others employing the antisheep hemolytic system deny or minimize the influence of natural antisheep hemolysin in the technic which they employ. Theoretically at least the presence of natural antisheep hemolysin in some human sera may be expected to disturb quantitative relations in the hemolytic system to a sufficient extent to reduce the delicacy of complement-fixation tests; the subject is one of primary importance and deserving of considerable study from the standpoint of standardization of the technic and the promotion of a test as sensitive as is consistent with practical specificity.

An antisheep hemolytic system is apparently used in the majority of laboratories and presumably is yielding satisfactory results insofar at least as the serologists are concerned; for this reason any evidence unfavorable to the antisheep system must be conclusive if this time-honored and well-tried system is to be discarded by those seeking to improve the quality of their work.

METHODS OF STUDY

The possible influence of natural antisheep hemolysin in human sera upon the Wassermann test may be studied by the following methods:

*This investigation was aided by funds accruing from the distribution of arsphenamine.

1. By testing the sera in graded doses before and after removal of the hemolysins.
2. By determining the influence upon the Wassermann reaction of varying and excessive amounts of rabbit antisheep hemolysin in the hemolytic system.
3. By testing sera containing natural antisheep hemolysin in graded amounts in a quantitative complement-fixation test to determine whether larger amounts of serum carrying relatively large amounts of natural hemolysin will give lesser degrees of complement fixation than smaller amounts of serum.
4. By using various methods for measuring the natural antisheep hemolysin in each serum and adjusting the hemolytic system accordingly.
5. By comparative complement-fixation tests with a large number of selected sera, employing the antisheep hemolytic system and such systems as the antihuman and antichickien.

PURPOSES OF INVESTIGATION

We have made rather extensive studies in this subject employing all five of these methods with three primary purposes in view:

1. To study the influence of natural antisheep hemolysins in heated human sera upon the results of complement-fixation tests conducted with fixed and varying amounts of serum.
2. To study the practical value of methods designed to remove or minimize the influence of natural antisheep hemolysin in human sera.
3. To determine on the basis of these actual experiences whether or not an antisheep hemolytic system may be used in a standardized complement-fixation technic.

The results of our studies with the first four of the above methods are summarized in this communication; the results of comparative tests with different hemolytic systems constituting the fifth method, are given in the succeeding paper.

METHODS FOR THE REMOVAL OF NATURAL ANTISHEEP HEMOLYSIN FROM HUMAN SERA

The usual method employed for the removal of natural antisheep hemolysin consists of inactivating the sera at 56° C. for thirty min-

utes, adding washed sheep corpuscles and centrifuging the mixture for corpuscle-free serum after standing an hour at incubator or room temperature. As Bauer^{1,2} described many years ago, this procedure may result in some sera acquiring anticomplementary properties well known as the "Sachs'-Friedberger phenomenon;" to avoid this unsatisfactory result, Rossi³ has advised the absorption of heated sera at a low temperature as follows: 1.5 c.c. of inactivated serum are placed in a chilled centrifuge tube, treated with 0.5 c.c. of thoroughly washed and chilled sheep corpuscles and the mixture placed in an ice chest for thirty minutes followed by rapid centrifuging with the tube surrounded with ice if the laboratory is quite warm.

Simon⁴ has recently described the following method: 0.4 c.c. of serum are inactivated for ten minutes at 56° C., intimately mixed with 1.6 c.c. of a 2.5 per cent suspension of washed sheep corpuscles and extracted for ten minutes at from 37 to 40° C. in a water-bath followed by centrifuging for corpuscle-free fluid which is now so diluted that each cubic centimeter contains 0.2 c.c. serum. He does not mention whether sera develop anticomplementary properties during this procedure and advocates this method of absorption of natural antish sheep hemolysin for conducting the Wassermann test with doubtfully reacting sera.

All methods for the removal of antish sheep hemolysin are too time-consuming and laborious for routine absorption of all sera and particularly the method described by Rossi, when the examination of 50 or more sera constitutes an ordinary day's work. We have attempted to simplify the procedure by heating specimens of whole blood at 56° C. for ten minutes, followed by the addition of washed sheep corpuscles and centrifuging after standing half an hour, but the resulting sera were unsatisfactory being too deeply discolored with hemoglobin due to the hemolysis of human corpuscles as a result of exposure to this temperature.

Numerous experiments conducted by us have confirmed the work of Simon that heating sera at 56° C. for ten minutes suffices to inactivate complement, and absorption for ten minutes in a water-bath at 38° C. is ample, the union of corpuscles and hemolysin being extraordinarily rapid and complete under these conditions. We regard the method of Simon as best for the removal of antish sheep hemolysin and have used it in all of our work, although sera have

occasionally acquired slight anticomplementary properties as a result of this procedure.

Mention may also be made in this connection of the absorption of sera with barium sulphate originally advocated by Wechsellmann⁵ as a means for increasing the sensitiveness of the Wassermann reaction by the absorption of complementoids. Noguchi and Bronfenbrenner⁶ have found that this procedure also removes natural antishoop hemolysin and syphilis antibody, results which were confirmed in these laboratories by Kyotoku.⁷

Absorption of sera with sheep corpuscles, however, does not appear to remove syphilis antibody and is the method of choice; the disadvantages are the time consumed, possible inaccuracy in exact dosage of serum and the development of anticomplementary substances in an occasional serum.

Part 1

THE INFLUENCE UPON THE WASSERMANN REACTION OF THE REMOVAL OF NATURAL ANTISHEEP HEMOLYSIN FROM HUMAN SERA

Various opinions have been expressed regarding the influence of natural antishoop hemolysins in human sera upon the results of Wassermann tests as determined by testing sera before and after absorption. Rossi³ in a study of sera from 60 cases of syphilis found 50 reacting positively whereas after removal of the hemolysins 56 sera yielded positive reactions; Jacobaeus⁸ in a study of 257 cases obtained 10 per cent more positive reactions after absorption of the sera with sheep corpuscles. Bailey⁹ advocates the removal of natural hemolysins from sera yielding negative or doubtful reactions which contain large amounts of hemolysin, but believes that otherwise the importance of these hemolysins is not great and particularly if a strong antigen is used in the tests. Olmstead,¹⁰ using the method of Rossi, found that of forty-seven sera yielding negative reactions before absorption, five or 10.6 per cent were positive after absorption and that these sera were from persons undoubtedly luetic or giving histories suspicious of syphilis. When the results of the Wassermann tests were read immediately after the second period of incubation instead of after standing in a refrigerator overnight, the results observed with plain and absorbed sera were quite similar and the excess of hemolysin represented by the natural

hemolysins in the human sera, made little difference. Van Saun¹¹ found the effect of natural antish sheep hemolysin in the Wassermann test a negligible factor, but advises the removal of these hemolysins from sera showing a very great excess when conducting the gonococcus complement fixation test. Ottenberg¹² found that of 144 negatively reacting sera containing a considerable excess of natural hemolysin, 36 sera became definitely positive when retested after absorption and in all there were good clinical grounds for suspecting syphilis. Simon⁴ advocates the removal of antish sheep hemolysins from sera yielding doubtful or partial reactions, as a means of disposing of these troublesome problems.

Using the method of Simon for the absorption of hemolysin, we have tested a large number of sera before and after removal of antish sheep hemolysins with the results summarized in Table I of sera which did not acquire anticomplementary properties during the procedure.

TABLE I
SUMMARY OF RESULTS OBSERVED IN WASSERMANN TESTS BEFORE AND
AFTER ABSORPTION OF ANTISHEEP HEMOLYSIN

SERA TESTED	PERCENTAGE SHOWING POSITIVE REACTIONS AFTER ABSORPTION	PERCENTAGE SHOWING STRONGER REACTIONS AFTER ABSORPTION	PERCENTAGE SHOWING NO CHANGE	PERCENTAGE SHOWING WEAKER REACTIONS AFTER ABSORPTION
110	3	35	62	None

Of these 110 sera only four, or about 3 per cent, gave a weakly positive result after absorption that reacted negatively before removal of the hemolysins; 35 per cent showed stronger positive reactions after absorption. In conducting these tests the results were read immediately after the second period of incubation; when the results were read after the tubes had stood overnight in a refrigerator two more sera containing natural hemolysin yielded negative reactions, whereas the same sera after absorption of the hemolysins yielded weakly positive reactions. In every instance so far encountered these sera were from persons undergoing treatment for syphilis and the results have shown that at least 3 to 5 per cent of sera containing small amounts of syphilis antibody may yield falsely negative reactions due to presence of natural hemolysin for sheep

corpuscles, and particularly if the practice of allowing the tubes to settle in a refrigerator overnight is adhered to.

Table II gives the results of tests with twenty sera in varying doses before and after absorption, as examples of our results; the

TABLE II

THE INFLUENCE UPON THE WASSERMANN REACTION OF REMOVAL OF ANTISHEEP HEMOLYSIN BY ABSORPTION WITH SHEEP CORPUSCLES

SERA	ABSORPTION	RESULTS			0.2 C.C. CONTROL	SERA	ABSORPTION	RESULTS			0.2 C.C. CONTROL
		0.2 C.C.	0.02 C.C.	0.002 C.C.				0.2 C.C.	0.02 C.C.	0.002 C.C.	
1	Before	++	-	-	-	11	Before	++	-	-	-
	After	+++	-	-	-		After	++	+	-	+
2	Before	++	-	-	-	12	Before	+	-	-	-
	After	+++	-	-	-		After	++	-	-	-
3	Before	+	-	-	-	13	Before	+	-	-	-
	After	++	-	-	-		After	++	-	-	-
4	Before	++++	++	-	-	14	Before	++++	++++	-	-
	After	++++	+++	-	-		After	++++	++++	-	+
5	Before	++++	++++	+	-	15	Before	+++	+	-	-
	After	++++	++++	+	++		After	++++	+++	-	-
6	Before	++++	+	-	-	16	Before	+++	-	-	-
	After	++++	++	-	++		After	+++	-	-	-
7	Before	++++	+	-	-	17	Before	++	-	-	-
	After	++++	+	-	-		After	++	-	-	-
8	Before	++	-	-	-	18	Before	++++	-	-	-
	After	++	-	-	-		After	++++	-	-	-
9	Before	+++	-	-	-	19	Before	++++	+	-	-
	After	++++	-	-	-		After	++++	++	-	-
10	Before	+++	-	-	-	20	Before	++++	++++	++	-
	After	+++	-	-	-		After	++++	++++	++++	+

influence exerted by the presence of natural antishoop hemolysin is not brought out by tests with strongly positive sera used in constant doses of 0.2 c.c. but rather with weakly reacting sera containing large amounts of natural hemolysin or with strongly reacting sera containing large amounts of hemolysin when tested in smaller doses.

TABLE III

THE INFLUENCE OF REMOVAL OF NATURAL ANTISHEEP HEMOLYSIN UPON QUANTITATIVE COMPLEMENT-FIXATION TESTS

SERA	ABSORPTION	COMPLEMENT FIXED						SERUM CONTROLS	
		2 UNITS	3 UNITS	4 UNITS	5 UNITS	6 UNITS	8 UNITS	1 UNIT	2 UNITS
1	Before	++++	++++	++++	++++	++++	-	-	-
	After	++++	++++	++++	++++	+++	-	-	-
2	Before	++++	++++	++++	++	-	-	-	-
	After	++++	++++	++++	+++	-	-	+	-
3	Before	+++	-	-	-	-	-	-	-
	After	+++	+	-	-	-	-	-	-
4	Before	++++	++++	++	-	-	-	-	-
	After	++++	++++	+++	-	-	-	-	-
5	Before	+++	+	-	-	-	-	-	-
	After	++++	+	-	-	-	-	-	-
6	Before	++++	++++	-	-	-	-	-	-
	After	++++	++++	++	-	-	-	+	-

As shown in Table II and also in Table III, the latter giving the results of a few comparative tests with the technic of Browning and McKenzie employing the sera in constant dose of 0.1 c.c. with increasing amounts of complement, some sera become more anticomplementary after absorption with sheep cells. In our experience this occurs to a slight extent with from 10 to 20 per cent of sera and may at times be responsible for the apparent increase in the

strength of the reaction rather than the removal of the natural hemolysin.

THE INFLUENCE OF ABSORPTION WITH SHEEP CORPUSCLES UPON THE
ANTICOMPLEMENTARY ACTIVITY OF SERA

Special studies of this phase of the problem were conducted by titrating the anticomplementary activities of sera in varying doses before and after absorption with sheep cells with an antihuman hemolytic system, an identical technic being maintained throughout. The results observed with a few sera are given in Table IV as examples; in this table are shown the smallest amounts of sera proving anticomplementary before and after removal of the natural hemolysins and of the eight sera listed, three showed that they had acquired anticomplementary activity as a result of absorption. These anticomplementary substances, however, are thermolabile inasmuch as heating the absorbed sera a second for ten minutes at 56° C. in a water-bath resulted in their removal.

TABLE IV

THE EFFECT OF ABSORPTION OF NATURAL ANTISHEEP HEMOLYSIN WITH
CORPUSCLES UPON THE ANTICOMPLEMENTARY ACTIVITY OF SERA

SERA	ANTICOMPLEMENTARY UNITS OF SERA		
	BEFORE ABSORPTION	AFTER ABSORPTION	AFTER ABSORPTION AND HEATING
1	0.05 c.c.	0.05 c.c.	0.1 c.c.
2	0.1 c.c.	0.05 c.c.	0.1 c.c.
3	0.1 c.c.	0.03 c.c.	0.2 c.c.
4	0.05 c.c.	0.05 c.c.	0.1 c.c.
5	0.05 c.c.	0.05 c.c.	0.1 c.c.
6	0.1 c.c.	0.05 c.c.	0.1 c.c.
7	0.05 c.c.	0.05 c.c.	0.1 c.c.
8	0.05 c.c.	0.05 c.c.	0.1 c.c.

For this reason proper caution must be exercised in conducting tests with absorbed sera unless reheated; the serum controls should carry slightly more serum than used with the antigen in order to detect this increase of anticomplementary activity of absorbed sera (Sachs-Friedberger phenomenon) which may not always become manifest in the serum control tube but be brought out in the presence of antigen and possibly result in falsely positive reactions of slight degree. Probably it would be a good practice to reheat all absorbed

sera at 56° C. in a water-bath for ten minutes although this may result in the destruction of more syphilitic antibody.

The general conclusions of this phase of the subject may be summarized as follows:

1. At least 3 to 5 per cent of sera containing small amounts of syphilitic antibody may yield falsely negative reactions with an antishoop hemolytic system due presumably to the presence of large amounts of natural hemolysins. These results are particularly apt to occur if the tubes are placed in an ordinary refrigerator overnight before the results are read.

2. The absorption of sera with sheep corpuscles is somewhat laborious if the practice of absorbing all negative and doubtfully reacted sera is adopted, and may result in rendering some of the sera slightly anticomplementary although this may be removed by reheating the absorbed sera for about ten minutes at 56° C.

Part 2

THE INFLUENCE UPON THE WASSERMANN REACTION OF EXCESSIVE AMOUNTS OF ANTISHEEP HEMOLYSIN

Another means of studying the influence of antishoop hemolysin in human sera upon the Wassermann test conducted with an antishoop hemolytic system, is to conduct comparative tests using varying and excessive amounts of immune hemolysin instead of the usual two units. Dexter and Cummer¹³ found in experiments of this kind that about 21 per cent of positively reacting sera may be made to yield negative or ambiguous reactions by the addition of large amounts of immune hemolysin. Neill¹⁴ found in a series of experiments that while natural antishoop hemolysin does reduce fixation when present in syphilitic sera, the amount of hemolysin must be quite considerable and the amount of syphilitic antibody very small in order to produce a significant effect. He concludes that the presence of antishoop hemolysin in sera is not a valid objection to the use of a sheep cell hemolytic system provided the sera are used in amounts corresponding to not less than 0.1 c.c. for a test with a total volume of 4 c.c. or 5 c.c.

We have conducted a large number of experiments to determine the influence upon the results of the Wassermann test with syphilitic sera of excessive amounts of antishoop hemolysin. In one set

of experiments each inactivated syphilitic serum was used in a constant amount of 0.1 c.c. in a series of seven test tubes with a cholesterolized extract of heart as antigen and after a primary incubation of one hour in a water-bath, hemolysin was added in amounts of one, two, four, six, eight and ten units with one unit in the antigen and serum control tubes. The hemolysin was so diluted that the unit was 0.1 c.c. in the hemolytic system employed. After a secondary incubation of about one hour the results were read and the tubes placed in a refrigerator with a second reading the following day. The results observed with 50 sera are shown in Table V; in preparing this table only such sera were included as yielded completely hemolyzed serum controls with one unit of hemolysin and the results are those observed after the tubes had stood in a refrigerator overnight.

TABLE V

THE INFLUENCE OF INCREASING AMOUNTS OF ANTISHEEP HEMOLYSIN UPON COMPLEMENT-FIXATION TESTS WITH SYPHILITIC SERA IN DOSES OF 0.1 C.C.

SERA	UNITS OF HEMOLYSIN						SERA	UNITS OF HEMOLYSIN					
	1	2	4	6	8	10		1	2	4	6	8	10
1	++	+	-	-	-	-	26	++++	++++	++++	++++	++++	++++
2	++	+	-	-	-	-	27	++++	++++	++++	++++	++++	++++
3	++++	++++	+++	+++	+++	+++	28	++++	++++	++++	++++	++++	++++
4	+	+	-	-	-	-	29	++++	++++	+++	++	+	+
5	++	+	+	+	-	-	30	++++	++++	++++	++++	++++	++++
6	++	+	+	-	-	-	31	++++	+++	+	+	-	-
7	+	+	-	-	-	-	32	+	+	-	-	-	-
8	++++	++++	++++	++++	++++	++++	33	++++	+++	+	-	-	-
9	++++	+++	+++	+++	+++	+++	34	++++	++++	++++	++	+	+
10	++++	++++	++++	++++	++++	++++	35	++++	++++	++++	++++	++++	++++
11	++++	+++	+++	++	++	++	36	++++	++++	++++	++++	++++	++++
12	+++	++	+	+	+	-	37	++++	++++	++++	++++	++++	++++
13	++	+	+	-	-	-	38	++++	++++	++++	++++	++++	++++
14	++++	+++	++	++	++	-	39	++++	+++	+	-	-	-
15	+++	++	-	-	-	-	40	++++	++++	++++	++++	++++	++++
16	+++	++	+	+	+	-	41	++++	++++	+++	++	++	+
17	++++	++++	++++	++++	++++	++++	42	++++	++++	++	++	++	++
18	++++	++++	++++	++++	++++	++++	43	++	++	-	-	-	-
19	+++	++	++	+	+	+	44	++++	+++	+++	+++	+++	+++
20	++++	+++	+++	+++	+++	+++	45	++++	++++	+++	+++	+++	+++
21	++++	++++	++++	++++	++++	++++	46	++++	+++	+++	+++	+++	+++
22	++++	++++	++++	++++	++++	++++	47	++++	++++	+++	+++	+++	+++
23	++++	+++	-	-	-	-	48	++++	+++	-	-	-	-
24	++++	++++	++++	++++	++++	++++	49	+++	++	-	-	-	-
25	++++	+++	+++	+++	+++	+++	50	++++	++++	++	+	+	+

These experiments have shown quite conclusively that with sera containing large amounts of syphilitic antibody, excessive amounts of hemolysin have practically no influence upon the results or at most reduce a ++++ to a +++ reaction; of much greater importance, however, is the profound influence exerted upon weakly positive sera and particularly when more than two units of hemolysin have been used, a large proportion of + and ++ reactions with two units of hemolysin becoming - or nearly so with four or more units of hemolysin, readings being made after the tubes have stood in a refrigerator overnight. Readings made immediately after complete hemolysis of the antigen and serum controls did not show such marked differences, although with the + and ++ sera, six or more units of hemolysin occasionally produced completely negative reactions.

TABLE VI
THE INFLUENCE OF INCREASING AMOUNTS OF ANTISHEEP HEMOLYSIN UPON
COMPLEMENT FIXATION WITH SYPHILITIC SERA

SERA	HEMOLYSIN	RESULTS WITH VARYING DOSES OF SERUM					
		0.2 c.c.	0.1 c.c.	0.01 c.c.	0.001 c.c.	0.0001 c.c.	0.2 c.c. control
1	1 unit	++++	++++	+++	+++	+	+
	2 units	++++	+++	++	-	-	-
	4 units	++++	+++	-	-	-	-
	6 units	++++	+++	-	-	-	-
	8 units	++++	+++	-	-	-	-
	10 units	++++	+++	-	-	-	-
	12 units	++++	+++	-	-	-	-
4	1 unit	++++	++++	++++	++	+	-
	2 units	++++	++++	+++	-	-	-
	4 units	++++	++++	-	-	-	-
	6 units	++++	++++	-	-	-	-
	8 units	++++	++++	-	-	-	-
	10 units	++++	++++	-	-	-	-
	12 units	++++	++++	-	-	-	-
6	1 unit	++++	++++	++++	++++	++	-
	2 units	++++	++++	++++	+++	+	-
	4 units	++++	+++	++	-	-	-
	6 units	++++	++	+	-	-	-
	8 units	++++	++	+	-	-	-
	10 units	++++	++	+	-	-	-
	12 units	++++	++	+	-	-	-
15	1 unit	+++	++	+	+	-	-
	2 units	+++	++	+	-	-	-
	4 units	-	-	-	-	-	-
	6 units	-	-	-	-	-	-
	8 units	-	-	-	-	-	-
	10 units	-	-	-	-	-	-
	12 units	-	-	-	-	-	-

Additional experiments were conducted with forty-two selected sera used in doses varying from 0.2 to 0.0001 c.c. with increasing amounts of hemolysin; the results observed with four of these sera are given in Table VI as examples of the readings made after the tubes had stood in a refrigerator overnight.

As shown in Table VI the use of four or more units of hemolysin had an influence upon weakly or moderately positive sera in doses of 0.2 to 0.1 c.c. which became more marked with the smaller doses of serum; with the strongly positive sera the influence of excessive amounts of hemolysin was slight with 0.2 and 0.1 c.c. doses of serum but became more marked with the smaller doses.

These experiments have shown, therefore, that while excessive amounts of antishoop hemolysin have practically no effect upon sera containing large amounts of syphilis antibody and tested in doses of 0.1 or 0.2 c.c. with a sensitive antigen, many weakly positive sera in doses of 0.1 or 0.2 c.c. are influenced to the extent that excessive amounts of hemolysin may dissociate or deflect sufficient complement to produce complete hemolysis or falsely negative reactions; these results are particularly apt to occur if the tubes are placed in an ordinary refrigerator overnight before the readings are made.

Part 3

THE INFLUENCE OF NATURAL ANTISHEEP HEMOLYSIN IN QUANTITATIVE COMPLEMENT-FIXATION TESTS

When human sera are tested in graded amounts with constant amounts of antigen and complement for the purpose of measuring the amount of syphilitic antibody the larger doses of weakly positive sera may yield less complement fixation than smaller doses, due in part to the presence of sufficient natural hemolysin in the larger amounts of serum to dissociate the complement from the antigen-antibody (syphilitic) complex; as stated this has been found especially true of weakly syphilitic sera and constitutes a serious drawback to the employment of an antishoop hemolytic system in any test designed as quantitative on the basis of varying the amounts of each serum employed.

Table VII gives the results observed with a few sera selected from a large series in which the larger amounts of serum gave more hemolysis than the smaller amounts; so far this has been found

only occasionally and with the sera of syphilitics containing relatively large amounts of natural antisheep hemolysin and yielding weakly or moderately positive Wassermann reactions.

TABLE VII

THE INFLUENCE OF NATURAL ANTISHEEP HEMOLYSIN UPON THE
RESULTS OF COMPLEMENT-FIXATION TESTS WITH WEAKLY
POSITIVE SERA IN VARYING AMOUNTS

SERA	ABSORPTION*	AMOUNTS OF SERUM					
		0.0125 c.c.	0.025 c.c.	0.05 c.c.	0.1 c.c.	0.2 c.c.	0.3 c.c.
11	Before absorption	—	—	—	++	+	—
	After absorption	—	—	+	++	++	++
55	Before absorption	—	—	—	—	+	+
	After absorption	—	—	—	—	++	++
82	Before absorption	—	—	+	++	++	+
	After absorption	—	—	+	+++	+++	+++

*Each serum contained sufficient natural hemolysin in 0.1 c.c. to produce complete hemolysis without the addition of immune hemolysin.

Results read after tubes had stood in a refrigerator overnight.

Part 4

METHODS FOR ADJUSTING THE ANTISHEEP HEMOLYTIC SYSTEM TO THE NATURAL ANTISHEEP HEMOLYSIN IN HUMAN SERA WITH THE DESCRIPTION OF NEW METHODS

Various methods have been proposed for the measure of natural hemolysin in human sera and the adjustment of the hemolytic system accordingly, in order to avoid the effects of excessive hemolysin as may result when the natural hemolysins are ignored and complement-fixation tests are conducted with fixed amounts of immune hemolysin. Bauer^{1, 2} originally advocated a method of conducting the complement-fixation test for syphilis utilizing the natural hemolysins alone as a means of simplifying the technic; Meirowsky,¹⁵ Noguchi,¹⁶ Swift¹⁷ and others have found the method unreliable or unsuitable. In our own experience with the Bauer method only 30 per cent of 264 heated sera in amounts of 0.1 to 0.2 c.c. contained sufficient natural hemolysin to produce complete hemolysis of 1 c.c. of a 2½ per cent suspension of sheep cells with 1 c.c. of 1:20 guinea pig complement. Other tests have been advocated along the same lines as that of Hecht as modified by Gradwohl, for the purpose of utilizing the natural hemolysins alone or in conjunction with the

complements of each serum, the results of our experiences with them being given elsewhere,¹⁸ but the special purpose of this phase of the present study was to determine the value of certain modifications of the Wassermann reaction advocated as means of dealing with the natural hemolysins in heated sera and minimizing their influence by adjustment of the hemolytic system.

The Kaliski Method.—Kaliski is credited with a modification of Bauer's method consisting of adding sheep corpuscles to all tubes after the primary incubation and reincubating for ten minutes; at the end of this time the degree of hemolysis in the serum control tubes is taken as an indicator of the presence of natural hemolysin in each serum and when hemolysis is but slight or has not occurred at all, immune antish sheep hemolysin is added, whereas if hemolysis is quite well along immune hemolysin is not added but dependence placed upon the natural hemolysin for the conduct of the test.

We have examined 264 sera with this method employing a cholesterolized extract of heart for antigen and have compared the results with those of our regular Wassermann tests conducted at the same time with the same antigen plus two additional antigens; the results were as follows:

1. Of the 264 sera, 79 or 30 per cent contained sufficient natural hemolysin in 0.2 c.c. of serum for the conduct of the test without the addition of immune hemolysin. Of these 79 sera, 80 per cent yielded results identical with the Wassermann reactions; 17 per cent yielded stronger positive reactions and 3 per cent yielded positive reactions in the Kaliski test with negative Wassermann reactions. The three sera yielding these results were from persons undergoing treatment for syphilis and the positive Kaliski reactions were apparently correct and a further indication that in the Wassermann test a large amount of natural antish sheep hemolysin in weakly syphilitic sera may yield erroneous negative results.

2. Of the remaining 185 sera receiving the usual two units of antish sheep hemolysin after ten minutes in the secondary incubation because the serum controls showed none or but slight hemolysis, 10, or about 5 per cent, of these sera yielded unsatisfactory serum controls, that is, hemolysis was incomplete; whereas in the regular Wassermann tests in which the same amount of hemolysin had been used but added with the cells immediately after the primary incuba-

tion, hemolysis in all controls was completed in a satisfactory manner.

Of the remaining 175 sera in which the results were satisfactory, 140 sera, or 80 per cent, reacted identically as in the Wassermann tests, and 35 sera, or 20 per cent, yielded somewhat stronger positive reactions in the Kaliski test.

In our opinion the Kaliski method serves to detect sera containing large amounts of natural antisheep hemolysin and thereby improves the delicacy of complement-fixation tests employing an antisheep system, but a distinct drawback is the unexplainable failure of complete hemolysis in the serum controls of at least 5 per cent of sera receiving immune hemolysin ten minutes after the addition of corpuscles. In our experience better results are secured by adding an additional tube to the regular Wassermann test carrying 0.2 c.c. serum, complement and corpuscles; at the end of the primary incubation if this tube shows complete hemolysis, immune hemolysin need not be added to the remaining tubes, but if hemolysis is not complete, the usual two units of hemolysin and corpuscles are added.

Method of Seelman.—Seelman¹⁹ has proposed a method for the adjustment of an antisheep hemolytic system to the natural hemolysins in human sera, consisting of the titration of antisheep hemolysin at the same time that tests are made of each serum for natural hemolysin and using in the main tests a sufficient amount of immune hemolysin to make one unit if the serum in dose of 0.05 c.c. does not contain the equivalent in natural hemolysin. The method appears to be satisfactory and has added considerably to the accuracy for the Wassermann test in Seelman's experience.

Method of Stern.—Stern²⁰ has proposed a method for the closer adjustment of the antisheep hemolytic system in order to avoid the effects of excessive amounts of hemolysin, consisting in the titration of immune antisheep hemolysin in the presence of the antigen and using one unit in the antigen tube of the Wassermann test with one and one-half units in the serum controls.

We have conducted a number of comparative tests to determine the value of this modification; the unit of antisheep hemolysin was invariably somewhat higher in the presence of antigen than when titrated in the usual manner.

Heated sera in varying doses were tested with our regular technic

and repeated at the same time with the same antigen after Stern's method; the results of a number of tests are shown in Table VIII.

TABLE VIII
THE INFLUENCE UPON THE RESULTS OF THE WASSERMANN TEST OF TITRATING ANTISHEEP HEMOLYSIN IN THE PRESENCE OF ANTIGEN (STERN)

SERA	REGULAR WASSERMANN TESTS				STERN METHOD				MODIFIED STERN METHOD WITH 2 UNITS HEMOLYSIN			
	0.01	0.1	0.2	0.2 C.C. CONTROL	0.01	0.1	0.2	0.2 C.C. CONTROL	0.01	0.1	0.2	0.2 C.C. CONTROL
2	+	++++	++++	-	+	++++	++++	-	-	++++	++++	-
3	+	++	+++	-	+	+++	+++	+	-	++	+++	-
4	+	+++	++++	-	+	++++	++++	-	-	+++	++++	-
5	+++	++++	++++	-	++++	++++	++++	-	++	++++	++++	-
6	+	++++	++++	-	++	++++	++++	-	++	++++	++++	-
7	+	++++	++++	-	++	++++	++++	-	-	++++	++++	-
8	+++	++++	++++	-	++++	++++	++++	-	++++	++++	++++	-
9	++	++++	++++	-	++++	++++	++++	-	++++	++++	++++	-
10	-	+	++++	-	-	+++	++++	-	-	+++	++++	-
11	-	-	+	-	+	+++	++++	+	-	+	+	-
12	-	+	++	-	-	++	+++	-	-	-	+	-
13	-	+	+++	-	+	+++	++++	-	-	+	++++	-
14	-	-	-	-	-	-	+	-	-	-	-	-
15	-	-	-	-	-	-	+	-	-	-	-	-
16	+++	++++	++++	+	++++	++++	++++	++	++++	++++	++++	-
17	++	++++	++++	-	+++	++++	++++	-	++	++++	++++	-
18	-	+	++	-	-	+	++	-	-	+	+	-
19	-	-	+++	-	+	+++	++++	+	-	-	++	-
20	-	-	-	-	-	+	+	-	-	-	-	-

As shown in this table, stronger reactions were frequently observed with the Stern method, but a serious error was found inasmuch as the sera of several normal nonsyphilitic individuals yielded weakly positive reactions (as sera 14, 15 and 20 in Table VIII); this error was particularly apt to occur with sera which were slightly anticomplementary, inasmuch as the one and one-half units of hemolysin in the serum control tubes may give complete hemolysis whereas the single unit in the antigen tubes resulted in partial inhibition of hemolysis due primarily to a deficient amount of hemolysin in the presence of anticomplementary serum.

Each test was repeated at the same time with two units of hemolysin as titrated in the presence of antigen, but as shown in Table VIII this amount of hemolysin was somewhat excessive, and, while

avoiding nonspecific results, rendered the tests somewhat less delicate than the regular tests.

New Methods for Adjusting the Hemolytic System to Natural Hemolysins in Human Sera.—For the accurate adjustment of the antishoop hemolytic system to each serum we have secured excellent results with the following technic:

For each serum ten test tubes are arranged and 0.1 c.c. heated serum placed in each; antigen is added to the ninth tube.

Antishoop hemolysin so diluted that the unit is about 0.5 c.c. of a given dilution when tested with 1 c.c. of 1:20 complement and 1 c.c. of 2½ per cent cell suspension is added to the first seven tubes in increasing amounts as 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 and 0.7 c.c.; 1 c.c. of a 2½ per cent suspension of sheep corpuscles are added to the first eight tubes and 1 c.c. of 1:20 dilution of complement to all of the ten tubes. The eighth tube is for natural hemolysin and the tenth tube is the serum control.

After primary incubation in a water-bath for one hour the unit of hemolysin is read off in the first eight tubes and two units added to the ninth and tenth tubes with 1 c.c. of 2½ per cent suspension of sheep corpuscles followed by reincubation for about one hour. If the eighth tube shows complete hemolysis so will all of the first seven tubes, indicating that 0.1 c.c. serum contains sufficient thermostabile natural hemolysin; in this case hemolysin is not added to the ninth and tenth tubes.

The antigen control receives two units of hemolysin on the basis of titration, that is, if the hemolysin is so diluted that the unit is 0.5 c.c. two units or 1.0 c.c. are added to this control.

The advantage of this method consists in the adjustment of the hemolytic system to the natural hemolysin in each serum; also if a serum is somewhat anticomplementary (as No. 26 in Table VIII) the unit of hemolysin will be higher so that the method permits the adjustment of the hemolytic system to the anticomplementary activity of each serum.

Examples of the arrangement of the test and the results observed with a few sera are shown in Table IX; further examples of the results with other sera are given in Table X. In a series of comparative tests with this method and the regular Wassermann tests, about 30 per cent of syphilitic sera yielded stronger reactions with the new method and from 3 to 5 per cent of sera from syphilitic

persons undergoing active treatment yielded positive reactions with the new method, whereas the regular Wassermann tests yielded negative reactions.

TABLE IX
THE TITRATION OF ANTISHEEP HEMOLYSIN IN THE PRESENCE OF EACH SERUM

SERA	HEMOLYTIC TITRATIONS								RESULTS		REGULAR WASSERMANN	
	1 0.1 c.c.	2 0.2 c.c.	3 0.3 c.c.	4 0.4 c.c.	5 0.5 c.c.	6 0.6 c.c.	7 0.7 c.c.	8 NONE	9 ANTIGEN	10 SERUM CONTROL	ANTIGEN	SERUM CONTROL
20	S*	M	M	C	C	C	C	S	++++	-	+	-
21	M	C	C	C	C	C	C	S	++	-	+	-
22	C	C	C	C	C	C	C	C	+++	-	++	-
26	S	S	S	M	M	M	C	N	++++	-	++++	+
34	M	C	C	C	C	C	C	S	+	-	-	-

* C.=complete hemolysis; M.=marked hemolysis; S.=slight hemolysis; N.=no hemolysis.

TABLE X
THE RESULTS OF COMPLEMENT-FIXATION TESTS IN SYPHILIS USING TWO UNITS OF ANTISHEEP HEMOLYSIN TITRATED IN THE PRESENCE OF EACH SERUM

SERA	REGULAR WASSERMANN TESTS*	SPECIAL WASSERMANN TESTS		
		UNIT OF HEMOLYSIN IN THE PRESENCE OF SERUM	ANTIGEN TUBE	SERUM CONTROLS
1	- ***	0.3	+	-
2	++++	0.1	++++	-
3	-	None**	+++	-
4	+	0.4	+++	-
5	++++	0.2	++++	-
8	-	None**	++	-
10	+	0.2	+++	-
12	++	0.3	++++	-
15	+	0.4	+++	-
18	+	0.3	++	-

*Conducted in usual manner with 2 units of hemolysin; 1 unit was 0.6 c.c. of 1:1000 dilution.

**No hemolysin added because 0.1 c.c. serum contained sufficient natural hemolysin.

***++++=strongly positive; +++ moderately positive, etc.

Tests were also conducted by the following method:

For each serum six test tubes were arranged carrying 0.1 c.c. heated serum in each. A 10 per cent suspension of washed sheep corpuscles was added to the first four tubes in increasing amounts as 0.2, 0.3, 0.4 and 0.5 c.c.

Two units of antsheep hemolysin previously titrated with 0.2 c.c. of the 10 per cent suspension of corpuscles and 1 c.c. of 1:20 dilution of mixed guinea pig serum complement, were added to all of the six tubes for each serum; antigen was added to the fifth tube of each series and complement to all.

After a primary incubation of one hour in a water-bath the corpuscle index of each serum was read off in the first four tubes, that is, the largest amount of corpuscle suspension completely hemolyzed by 0.1 c.c. of serum with two units of hemolysin, and one-half this amount of corpuscles were added to the fifth and sixth tubes for each serum followed by reincubation for about an hour.

The arrangement of this test is shown in Table XI as likewise the results observed with a few sera as compared with those of the regular Wassermann test.

TABLE XI
ADJUSTMENT OF THE ANTISHEEP HEMOLYTIC SYSTEM IN THE PRESENCE OF EACH SERUM BY TITRATION WITH INCREASING AMOUNTS OF SHEEP CORPUSCLES

SERA	CORPUSCLE TITRATION *				SPECIAL TESTS		REGULAR TESTS	
	1 0.2	2 0.3	3 0.4	4 0.5	5 ANTIGEN	6 SERUM CONTROL	ANTIGEN	SERUM CONTROL
1	C**	C	M	M	++++	-	+++	-
4	C	C	C	M	++	-	+	-
7	C	C	M	M	-	-	-	-
11	C	M	M	M	++++	-	++++	-
15	C	M	M	M	++++	-	+++	-
16	C	C	C	M	+	-	-	-
19	C	M	M	M	++++	-	++++	-
20	C	C	C	M	++++	-	++++	-
22	C	C	C	M	++	-	+	-
24	C	C	M	M	+++	-	+++	-

* Titration of 10 per cent suspension of sheep cells in presence of 0.1 c. c. heated sera, two units of hemolysin and complement.

** C. = complete hemolysis; M. = marked hemolysis.

The advantages of this method are similar to those found with the method described above, namely, a more accurate adjustment of the hemolytic system than is possible with the regular Wassermann test and a means of adjustment of the hemolytic system for anticomplementary sera; the results were also quite similar, that is, greater degrees of complement fixation with syphilitic sera were

frequently observed as likewise the occasional positive reaction with serum containing small amounts of syphilis antibody and yielding negative reactions in the regular tests.

SUMMARY AND CONCLUSIONS

1. The results of complement-fixation tests with strongly positive sera in amounts of 0.1 to 0.2 c.c. and an antisheep hemolytic system are not influenced by the presence of natural antisheep hemolysins in the sera; however, sera containing relatively small amounts of syphilis antibody and large amounts of natural hemolysin may yield falsely negative reactions unless the natural hemolysins are removed. In a series of tests this occurred with 3 to 5 per cent of such sera.

2. If complement-fixation tests conducted with an antisheep hemolytic system are read immediately after the secondary period of incubation the influence of natural hemolysins upon weakly positive sera in producing falsely negative reactions is not as evident as when the readings are made after the tubes have stood in a refrigerator for sixteen hours or longer.

3. Quantitative complement-fixation tests conducted with varying amounts of patient's serum may be disturbed and rendered inaccurate by the presence of large amounts of natural antisheep hemolysin and particularly with sera containing small amounts of syphilis antibody.

4. While excessive amounts of rabbit immune hemolysin have no influence upon the results of tests conducted with strongly positive sera used in amounts of 0.1 to 0.2 c.c., four or more units of hemolysin may profoundly influence the results of tests with weakly positive sera and with strongly positive sera used in smaller amounts.

5. The removal of natural antisheep hemolysins from human sera by absorption with sheep corpuscles may render some sera slightly anticomplementary but these antilytic substances may be removed by heating the absorbed sera for ten minutes at 56° C.

6. Methods designed for adjusting the antisheep hemolytic system to the natural hemolysins in human sera in order to avoid an excess of hemolysin, have usually increased the delicacy of tests for syphilis antibody. New methods for this purpose are described.

7. The general conclusions of this part of the study are:

(1) The natural antisheep hemolysins in some human sera and particularly in those containing small amounts of syphilis antibody may influence the results of complement-fixation tests conducted with an antisheep hemolytic system and yield falsely negative reactions with a small percentage of sera.

(2) These natural hemolysins may be removed by absorption with sheep corpuscles or their influence minimized by special methods and these means should be employed with practically all sera yielding doubtful or negative reactions to secure best results with an anti-sheep hemolytic system.

(3) The antisheep hemolytic system is not well adapted for a quantitative complement-fixation test based upon the use of varying amounts of patient's serum.

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A RAW SERUM WASSERMANN TEST EMPLOYING THE SHEEP HEMOLYTIC SYSTEM

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IT has been shown that a portion and sometimes all of the substances in syphilitic blood which are responsible for a positive Wassermann reaction may be destroyed when subjected to heat at 56° C., as is done in the classical test. This seems to be especially true in syphilis of the skin and nervous system and in latent syphilis; consequently a considerable percentage of these cases remains undetected when the test is made with inactivated serums alone. In order to avoid this source of error and to render the test more delicate, many efforts have been made to devise a satisfactory modification for testing serum in the noninactivated or "raw" state.

A careful review of the literature on the subject leads me to the conclusion that the majority of syphilographers, while admitting the greater delicacy of a raw serum test, are reluctant to accept its unsupported verdict as final in the diagnosis of syphilis because of the probability of a certain percentage of error on the positive side. The test is used, therefore, chiefly as a control in the treatment of syphilis. That this stand is well taken will be granted by any laboratory worker who is familiar with raw serum methods and their shortcomings.

One of the best known of these methods is the Hecht-Weinberg. It has become evident, however, that this method is inadequate because it fails to take into account the considerable variations in native complement and native amboceptor present in different human serums. Brendel¹ attempted to overcome this objection by a modification which provides a preliminary titration of the hemolyzing power of each serum. Besides being cumbersome, this method is not accurate, as the titration determines only the total hemolyzing index and gives no information whatever as to the relative complement or native amboceptor content of the serum ex-

amined. The method of Brendel was later modified in this country by Burdick,² and still later by Gradwohl,³ and has come to be known as the Hecht-Gradwohl modification.

In this country Noguchi's original modification is, I believe, the best known and most widely used raw serum test, and while it is, apparently, quite reliable, it has the disadvantage of employing a homohemolytic system.

Noguchi's later method has many sources of error which I have pointed out elsewhere.⁴

It would be a fruitless undertaking to attempt to consider in detail the many raw serum tests that have been devised by different workers. All of them, at least all with which I am familiar, have failed to take into consideration either one or more of the following major sources of error:

(a) Variations in the native complement content of human serums.

(b) Variations in the native antish sheep amboceptor content of human serums (very important when the sheep hemolytic system is employed).

(c) Variations in nonspecific complement absorption by different serums.

I have devised a method employing the sheep hemolytic system which corrects all these major sources of error, and does not require an amount of work inconsistent with the practical requirements of routine laboratory procedure.

It must be apparent that with these major sources of error adequately controlled a raw serum test will become as safe against false positives as an inactivated serum test, and will have the advantage of being more delicate, showing up more definite positives in cases of syphilis, and giving a greater negative value to negative reactions.

The test which I have devised includes a preliminary titration, the purpose of which is to determine: (a) the amount of native amboceptor in each serum; (b) the amount of guinea pig complement which must be added to each serum in order to have a standard quantity available for the test, making due allowance for the native complement and for nonspecific fixation of each serum under examination.

In the following description and in my tables I have followed

the suggestion of Ottenberg,⁵ that for the sake of uniformity, all work on the Wassermann test be reported in full Wassermann quantities. In our laboratory the test is done in one-fourth Wassermann quantities, and these amounts lend themselves to convenient and rapid measurement with special nipple pipettes of my own design and construction. Once accustomed to the use of nipple pipettes, one can work much more rapidly and even more accurately than with the usual graduated suction pipettes, and furthermore, they are cleaner and more sanitary. These nipple pipettes are made from ordinary 5 or 6 mm. glass tubing drawn out to suitable lengths, calibrated with mercury and marked. The markings are made with china paint and a fine brush; after the paint is dry, it is burnt into the glass in a Bunsen flame. Fine pipettes are laid on a screen and then held over the flame, as otherwise they will bend before the necessary degree of heat has been attained. We use the following pipettes (one-fourth Wassermann quantities): one pipette for each serum to be examined, marked at .025 and .05 c.c.; one .5 c.c. complement pipette, graduated into .025 c.c.; one .2 c.c. amboceptor pipette, graduated into .02 c.c.; one corpuscle pipette marked at .125 c.c. and .25 c.c. In addition to the above suitable pipettes and graduated cylinders for making up dilutions of complement, amboceptor, and corpuscles are necessary.

TECHNIC OF PRELIMINARY TITRATION

A preliminary titration is set up as shown in Table I. Row 1 in this set-up is a guinea pig serum titration. The object of Rows 2 and 3 is to determine the amount of native amboceptor present in the unknown serums. Row 2 is practically an amboceptor titration, the tubes in this row receiving complement, corpuscles and increasing amounts of amboceptor. The tubes in Row 3 receive complement, corpuscles, and the unknown serums, but no amboceptor. The only amboceptor in the tubes of Row 3, then, is that which is natively present in each serum, and the degree of the ensuing hemolysis in each tube will depend on the amount of such native amboceptor. By comparing the tubes of Row 3 (the unknown) from time to time, during the course of the incubation, with the tubes of row 2, (the known amboceptor amounts) it is possible to closely estimate the amount of native amboceptor present

in each serum to be tested; i. e., each tube of Row 3 has an amboceptor value corresponding to that tube of Row 2, which it most nearly approaches in rate of hemolysis.

It will be noticed that in these two rows of tubes a considerable excess of complement is used. This is done to overcome the disturbing effect of the varying amounts of native complement present in different raw serums. In the presence of an excess of complement further increments no longer influence hemolysis and, therefore, varying quantities added in the form of native complement to an already present excess will have no influence on the rate or degree of hemolysis. The amount of serum and corpuscles in these two rows are reduced to one-half in order to obtain the effect of complement excess with a minimum of complement. As the subsequent procedures are made in full Wassermann quantities, this must be allowed for in the calculations.

Rows 4 and 5 determine the amount of complement which must be added to each serum in the test proper in order to bring the available complement up to a uniform standard amount. Coincident with the amboceptor determination, complement and serum are incubated in these two rows as shown in the table, to permit non-specific fixation to take place. At the end of the half-hour period corpuscles and amboceptor are added. The amount of amboceptor to be added to each serum is dependent on the outcome of the amboceptor determination which at this time has been completed in Rows 2 and 3. The tubes are examined at the end of 5, $7\frac{1}{2}$, 10, $12\frac{1}{2}$, 15, 20, 25, and 30 minutes, and the time when complete hemolysis takes place in each individual tube, or the amount of inhibition at the end of thirty minutes is noted. The amount of complement which must be used in the test proper is then ascertained by reference to Table II, as follows: if hemolysis is completed in a tube in Row 4 in ten minutes or less, then part "A" of the table is referred to in order to find the proper dose. If a tube in Row 4 does not hemolyze within ten minutes, then the hemolyzing time is obtained on the corresponding tube in Row 5 and part "B" of the table is referred to. If a tube in Row 5 is not completely hemolyzed at the end of the half-hour, then part C of the table is referred to. It has been found that by employing two rows of tubes one receiving .2 c.c. complement and the other twice this amount, it is possible to make a more accurate approximation of the proper

complement allowance for the test than if the estimations are made with only one row of tubes.

The variations in complement strength of different guinea pig serums is a factor which had to be taken into consideration in working out this test. For the purposes of the amboceptor determination (Rows 2 and 3) variations in complement strength make no difference because there is an excess of complement in both rows of tubes. But in making the complement estimate, the factor of variations of the strength of guinea pig serum must be considered, for it is obvious that the allowance must be greater when the complement is weak than when it is strong. Of course, one could do a complement titration preliminary to the native complement determinations and make allowances accordingly. But this would take at least an additional hour's time which means a great deal in routine laboratory work. To obviate this, I proceed directly with the native complement determinations and introduce coincidentally with it a complement titration (Row 1). The subsequent complement allowances are then varied in accordance with the outcome of this titration. These variations are shown in Table II. The figures given in this table are the result of a large number of experimental tests, and bring the hemolyzing time in the test proper to approximately ten minutes.

It will be observed that when the amount of complement to be added is small, the difference for complement serums of different strengths is little or nothing. The reason for this is that when most of the work is done by the native complement and but little guinea pig serum needs to be added, the usual variations in the strength of the latter make little practical difference. It is also obvious that when complement serum is weak, hemolysis in Rows 3 and 4 is correspondingly slower and this will automatically bring the complement allowance estimate higher. It is for this reason that the variations in complement allowances shown in the table are not in the same ratio as the variations in titer of guinea pig serum.

TECHNIC FOR TEST

The set-up for the test proper is the same as for the classical test, except that raw serum is used and the amount of complement and amboceptor for each serum is varied in accordance with the

TABLE I

	ROW			NEGATIVE CONTROL	POSITIVE CONTROL	UNKNOWN			
Native Complement Determination	5	1st Incubation	Comp.	0.4	0.4	0.4	Three additional tubes are set up for each unknown serum to be tested.		
			Serum	0.2	0.2	0.2			
		2nd Incubation	Ambo.	*	*	*			
			Corp.	1.0	1.0	1.0			
	4	1st Incubation	Comp.	0.2	0.2	0.2			
			Serum	0.2	0.2	0.2			
		2nd Incubation	Ambo.	*	*	*			
			Corp.	1.0	1.0	1.0			
Native Amboceptor Determination	3	1st Incubation	Comp.	3.0	3.0	3.0			
			Serum	0.1	0.1	0.1			
			Ambo.	0	0	0			
			Corp.	0.5	0.5	0.5			
	2	1st Incubation	Comp.	3.0	3.0	3.0	3.0	3.0	3.0
			Serum	0	0	0	0	0	0
			Ambo.	0†	0.04	0.08	0.12	0.16	0.20
			Corp.	0.5	0.5	0.5	0.5	0.5	0.5
Guinea Pig Complement Titration	1	1st Incubation	Comp.	0.2	0.4	0.6	0.8	1.0	1.2
			Serum	0	0	0	0	0	0
		2nd Incubation	Ambo.	0.1	0.1	0.1	0.1	0.1	0.1
			Corp.	1.0	1.0	1.0	1.0	1.0	1.0

*Amount depends on outcome of amboceptor determination in Rows 2 and 3.

†To control small amount of native antiship amboceptor which may be present in guinea pig serum.

Note

Antiship amboceptor dilution must be of such strength that 0.4 c.c. represents approximately eight Wassermann units.

Complement dilution is 1:10; corpuscle suspension 5 per cent.

All tubes are brought up to 5 c.c. with salt solution.

Leave Rows 2 and 3 at room temperature for ten minutes before placing in the bath. During this time the tubes with high amboceptor values will hemolyze and can be compared and eliminated. If tubes are placed in the bath at once these high amboceptor tubes will hemolyze so rapidly that comparisons are difficult.

If test is made in one-fourth above quantities the amounts lend themselves to convenient measurement with pipettes as described in the text, and a considerable saving of material is effected.

(Cont'd on p. 163)

findings of the preliminary titrations as above described. An acetone-insoluble lipid antigen must be used, which has previously been titrated as for the classical test. Incubation is discontinued and a final reading made on each serum five minutes after the serum control is hemolyzed, or about fifteen minutes after the test has been placed in the bath. The controls will all hemolyze within two or three minutes of each other, these negligible differences being due to the slight unavoidable differences in measurements of ingredients which go with even the most careful technic. In the classical test the controls hemolyze in anywhere from fifteen minutes to one hour, representing large differences in available complement due largely to differences in nonspecific fixation by different serums.

The test I have described has the following advantages:

It employs noninactivated serum.

A sheep hemolytic system is used as indicator.

Native complement, native amboceptor, and nonspecific fixation are allowed for; as a result amboceptor and complement are uniform for all serums in the final test.

While the allowance of complement finally available in the test precludes the possibility of false positives, the specific delicacy of the test is still such as to give about 15 per cent more definitely

Example

Hemolysis in the negative control tube in Row 3 was equal, let us say, to that tube in Row 2 containing .12 c.c. amboceptor; therefore .1 c.c. of the negative control serum has an amboceptor value equal to .12 c.c. amboceptor dilution and .2 c.c. (the amount to be used in the test proper) has a value equal to .24 c.c. The full amboceptor dose for the test being .4 c.c. it will be necessary to add in subsequent procedures the difference between .4 c.c. and .24 c.c. or .16 c.c. amboceptor dilution to the negative control serum in order to bring it to the full amboceptor value.

Hemolysis in the positive control tube in Row 3 equalled, let us say, that tube in Row 2 containing .2 c.c. amboceptor. One-tenth c.c. of this serum, therefore, has an amboceptor value equal to .2 c.c. amboceptor and .2 c.c. has a value of .4 c.c.; as this is the full amboceptor dose, no amboceptor need be added to this serum in the subsequent procedures.

Hemolysis in the unknown serum in Row 3 equalled the tube in Row 2 containing no amboceptor whatever. The hemolysis which did take place, if any, therefore, was due to the slight amount of sheep amboceptor sometimes present in guinea pig serum. The unknown, therefore, contains no amboceptor whatever and in all subsequent procedures the full dose of amboceptor must be added to it.

In the complement determination, then, we give the Negative Control Serum .16 c.c. amboceptor dilution, the Positive Control Serum no amboceptor whatever and the Unknown Serum the full dose or .4 c.c.; we add corpuscles and proceed to incubate. We find that the negative control tube in Row 5 is just completely hemolyzed in about 15 minutes. Referring to part B of Table II we ascertain that this serum (assuming that the complement titration for the guinea pig serum used fell on .4 c.c.) must receive .6 c.c. complement in order to bring it up to the standard hemolyzing time of ten minutes. The positive control tube in Row 4 was hemolyzed completely in $7\frac{1}{2}$ minutes and referring to part A of Table II we find that this serum is to receive only .15 c.c. complement in the test. The unknown serum in Row 5 showed about 25 per cent inhibition at the end of the half hour; referring to part C of Table II we find that this serum must receive 1.4 c.c. complement in the test.

The set-up for the test proper for these serums will be as shown in Table III.

TABLE II

COMPLEMENT TITER	A			B									C				
	HEMOLYZING TIME IN MINUTES WITH 0.2 C.C. COMPLEMENT			HEMOLYZING TIME IN MINUTES WITH 0.4 C.C. COMPLEMENT									INHIBITION AFTER ½ HOUR				
	5	7½	10	5	7½	10	12½	15	20	25	30		5%	10%	25%	50%	75%
0.3	0.1	0.15	0.2	0.2	0.2	0.4	0.4	0.5	0.6	0.7	0.8		0.9	1.0	1.2	1.4	1.6
0.4	0.1	0.15	0.2	0.2	0.2	0.4	0.5	0.6	0.7	0.8	0.9		1.0	1.2	1.4	1.6	1.8
0.5	0.1	0.15	0.2	0.2	0.3	0.4	0.5	0.6	0.8	0.9	1.0		1.2	1.4	1.6	1.8	2.0
0.6	0.1	0.15	0.2	0.2	0.3	0.4	0.6	0.8	0.9	1.0	1.2		1.4	1.6	1.8	2.0	2.2
0.8	0.1	0.15	0.2	0.2	0.3	0.4	0.6	0.8	1.0	1.2	1.4		1.6	1.8	2.0	2.2	2.4

TABLE III

		SYSTEM, CORPUSCLE AND ANTIGEN CONTROLS		NEGA- TIVE CONTROL	POSITIVE CONTROL	UNKNOWN
1ST INCUBATION	Comp.	0	0	0.6	0.025	1.4
	Serum	0	0	0.2	0.2	0.2
	Antigen	UNIT	0	0	0	0
2ND INCUBATION	Ambo.	0	0.4	1.6	0	0.4
	Corp.	1.0	1.0	1.0	1.0	1.0
1ST INCUBATION	Comp.	*	*	0.6	0.025	1.4
	Serum	0	0	0.2	0.2	0.2
	Antigen	0	UNIT	UNIT	UNIT	UNIT
2ND INCUBATION	Ambo.	0.4	0.4	1.6	0	0.4
	Corp.	1.0	1.0	1.0	1.0	1.0

*1½ units as determined by the complement titration. It has been found experimentally that with this amount of complement and eight units of amboceptor hemolysis will be completed in about ten minutes.

positive reactions in cases of syphilis than does the classical Wassermann.

With all these advantages the test requires only very little more time for its performance than the classical test, and much less time than many other raw serum tests, such as, for instance the Hecht-Gradwohl.

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THE USE OF THE PHRASE "WASSERMANN REACTION"

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IN a recent article Vedder¹ states "that the use of the term Wassermann Reaction should be discontinued. The test is really an application of the Bordet-Gengou reaction, and Wassermann's ideas as to the specificity of the luetic antigen have been discarded long ago, together with most of the technic described by him." Gay² does not agree with this argument and states while Wassermann's original ideas regarding the nature of his test have proved in error, yet he is "entitled to credit for developing a novel type of nonspecific fixation reaction of great practical utility." Gay believes, however, that now is the suitable time for eliminating incorrect hypotheses and terms in immunology riveted on our literature by successful German propaganda.

Regarding the use of the term "Wassermann Reaction," I believe that it is employed altogether too freely and loosely and has really come into use as a synonym for *complement fixation in syphilis*; the phrase is rather carelessly applied by many persons to any complement-fixation test for syphilis regardless of how remote the technic may be from Wassermann's test described in 1906. On the other hand the test should not receive the designation "Bordet-Gengou reaction" although based upon the principles discovered by Bordet³ through an argument with Ehrlich on the multiplicity of complements, inasmuch as Wassermann, Neisser, and Bruck were the first to utilize the phenomenon in the serologic diagnosis of syphilis,⁴ just as Widal and Grünbaum first turned the discoveries of agglutinins to practical use in the diagnosis of typhoid fever. I have always believed, however, that the name of *Detre* was deserving of more mention in connection with the complement-fixation test for syphilis, inasmuch as he was working independently of Wassermann and published his results just ten days⁵ after Wassermann and his colleagues.

As stated above, the term "Wassermann" is used by most persons

as a short term for the phrase "complement-fixation test for syphilis," but this is an error and the term should be limited to the test conducted after the method of Wassermann. As far as I can ascertain, Wassermann has made no important changes in his technic as described in his early papers and still uses salt solution extracts of syphilitic liver for antigen although he can not have failed to note the success of alcoholic extracts of normal tissues and indeed, the general superiority of these extracts; apparently he continues to use the same hemolytic system and the same general technic described in 1906 and 1907. The term "Wassermann Reaction," therefore, should, strictly speaking, be confined to a test conducted with Wassermann's original technic, but practically, the latitude may be broader and embrace those modifications employing alcoholic extracts of luetic and nonluetic tissues as antigens and such changes as using each constituent of the test in one-half, one-quarter or one-tenth the amounts of the original Wassermann test inasmuch as these changes do not alter the principles and are used mainly for economy.

However, all tests employing a different method for adjusting the hemolytic system, a method for titrating complement, a different hemolytic system, the use of active instead of heated serum, the utilization of natural complements and amboceptors in patients' sera, etc., can not claim the designation "Wassermann test," being based upon principles and technic too remote from Wassermann's technic; modifications of this nature are now quite numerous and if the term "Wassermann Reaction" as a synonym for "complement-fixation test for syphilis" is to be dropped, as it should be, these modifications must be designated by the names of their discoverers; this is regarded by many of the profession as objectionable and confusing although possibly highly gratifying to the authors themselves so signally honored.

Finally it would appear advisable to exercise more care in the use of the terms "reaction" and "test;" in common with the majority of persons, I have used the terms as synonymous but believe that the term "test" should be used in designating the *technic or method* as "a means of trial," and "reaction" for expressing the *results* of the test; for example, a serum is submitted to a laboratory

for the "Wassermann test" and the results designated as the "reaction," as "a positive or negative Wassermann reaction."

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Abstract of Current Syphilis Literature

It is the purpose of this JOURNAL to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Wm. H. Deaderick, Dugan-Stuart Bldg., Hot Springs, Arkansas.

WM. H. DEADERICK, M.D., EDITOR

SYPHILIS, AN INESTIMABLE FACTOR IN INDUSTRIAL INEFFICIENCY.—Edward A. Oliver, Chicago. *Journal of Industrial Hygiene*, 1919, vol. 1, p. 246.

The cases which the author enumerates ought to be enough to make the industrial physician realize that this nation-wide campaign against the venereal diseases is his fight. The program here outlined for industrial physicians to follow is, in many features, similar to that carried out by the army in the war. Under this program the annual venereal disease rate in the army has dropped from 83.6 per 1000 in 1915 to 20 per 1000 in 1918. The program embraces four parts: 1. Educational and social measures similar to those carried out by the Commission on Training Camp Activities. 2. Prophylaxis after exposure. 3. Medical examination of employees. 4. The treatment of syphilis. By following out some such scheme as has been indicated in this article, industrial physicians can play a large and important part in this campaign against syphilis, an inestimable factor in industrial inefficiency.

STUDY IN A FOUNDLING INSTITUTION TO DETERMINE THE INCIDENCE OF CONGENITAL SYPHILIS.—L. R. DeBuys and Maud Loeber, New Orleans. *Journal of the American Medical Association*, 1919, vol. lxxiii, p. 1028.

The Wassermann reactions and luetin tests were shown to have been performed accurately, as was proved by the controls made. The negative Wassermann reactions in every case investigated may be explained by the intensity of the treatment to which each child had been subjected, or it may be that the bloods had not yet become positive. The luetin test in this series proved of greater value as a diagnostic measure than the Wassermann reaction in detecting

cases of congenital syphilis, and the clinical findings were of greatest value at that time when the value of the luetin was at its minimum, namely, in the first few weeks. The effect of the iodids on the luetin reaction was again shown in this study. The lesion is characteristic and can not be confounded with the normal positive luetin reaction. Because of the ages of those examined and the character of the institution, this investigation afforded an excellent opportunity to study the various available means of detecting the existence of congenital syphilis. Seventy-four and six tenths per cent were infants up to the age of 2 years, of whom 41.6 per cent were under 1 year of age. Congenital syphilis was found to be relatively more frequent in the illegitimate than in the legitimate children. Of course, this series does not constitute a fair criterion for a comparison of the Wassermann and luetin reactions. It does, however, afford a good idea of their relative values in connection with congenital syphilis at this time of life. It must be remembered that the mortality from congenital syphilis is very great, and that those cases in which the earliest ravages of the disease are escaped are those of less severe infection, or are those in which the patient has been partially or thoroughly treated. This study, therefore, we believe to be a fair test of the relative merits of the two reactions under these circumstances. The existence of skin eruptions of syphilitic origin in cases in which both Wassermann and luetin reactions were negative is of decided interest, and further emphasizes the necessity of employing all available means, including complete physical examination and laboratory tests, before deciding a case to be syphilitic or nonsyphilitic. The skin eruptions were more frequent the younger the subject. This was especially true of the syphilitic skin eruptions; twelve of the total of twenty-two instances of it were found within the first three months of life. Ten cases of positive syphilitic skin eruptions were detected at this time in which the luetin reaction had been negative. The syphilitic skin eruptions seemed to be of greatest diagnostic value at that time when the negative laboratory tests are most likely. With very few exceptions, all of the inmates of the institution were below the normal averages in weight, height, development and nutrition. This is of interest in view of the constitutional background of the inmates. Enlarged livers, spleens and glands appeared to be the most constant of the clinical evidences of congenital syphilis. The infrequency of the other clinical manifestations of congenital syphilis in this study, such as snuffles, fissures, wig, and scaling palms and soles, may have been influenced by the system of routine treatment in vogue in the institution as the cases were not followed by us from birth. The incidence of congenital syphilis in this institution, as revealed by the study, was 83.96 per cent. Seventy-nine cases, or 74.53 per cent, were shown by means of the luetin

reaction and ten cases, or 9.43 per cent, were shown by the clinical findings, revealing syphilitic skin eruptions. Many of the other cases classified as doubtful or negative had certain of the clinical symptoms of congenital syphilis, but not sufficient to warrant a positive diagnosis.

A SECOND ATTACK OF SYPHILIS TWO YEARS AFTER THE FIRST.—Jay Frank Schamberg, Philadelphia. *Journal of the American Medical Association*, 1919, vol. lxxiii, p. 826.

This case is all the more remarkable in view of the fact that the patient was irregular in his attendance at the University Hospital and that, through neglect, he developed what were, in all likelihood, evidences of an early meningeal involvement, characterized by headaches, inequality of the pupils, and exaggerated patellar reflexes. It is interesting to observe that not a vestige of immunity against the second attack remained. Indeed, the second attack was more severe than the first, and the Wassermann reaction bids fair to be more resistant to treatment. In this case, the evidence of a second attack is, in my opinion, indisputable. The author believes that the deduction that the patient was cured of his first attack is warranted by all of the facts. Cases of this character are more instructive in the light they throw on the curability of syphilis. The excellent pathologic researches of Warthin at Ann Arbor were persuading many physicians to believe in the dictum enunciated many years ago (under a different therapeutic regimen), "Once a syphilitic, always a syphilitic." The author believes that we are in a position at the present day, with more powerful and scientific drugs at our command, to state that syphilis is a curable disease. The criteria of cure are difficult to establish, because the evidential value of negative Wassermann tests is not conclusive. In view, however, of cures such as the one above reported, we may perhaps place more faith in repeatedly negative serologic tests and the absence of symptoms as indications of probable cure.

ONE HUNDRED CASES OF EARLY SYPHILIS IN MADAGASCAR SHARP-SHOOTERS.—Morin. *Journal de médecine de Bordeaux*, 1919, August 25, p. 331.

Syphilis is very common in Madagascar, and is regarded quite differently from its reception in Europe. Mild cases are frankly admitted, and are treated with herbs or other domestic remedies. Far from avoiding a contaminated individual, men are anxious to impregnate a syphilitic girl as soon as she recovers from the infection. Such girls are in demand, and are offered as brides by their parents with the serious, if naïve, guarantee that they have already had syphilis. However, these views are now limited to the lower

classes of the people. Congenital syphilis is wide-spread, and tertiary symptoms of all kinds are a matter of common observation. On the other hand, a diffuse eruption invests the disease with a shameful, inadmissible character.

In four months, the author observed over 150 cases of syphilis in Madagascar sharpshooters, including 35 cases of primary sore alone; 30 cases of concomitant, primary and secondary symptoms; 46 cases of only secondary symptoms; making 111 cases of recent syphilis. In these natives, where the entire color-scale from black to white is represented, it is often difficult to discover the moderate erythema of secondary syphilis, leaving out of consideration the skin affections of all kinds which frequently accompany this erythema. Of the 35 cases of typical hard chancres, treated by the author, 28 were situated on the glans or the prepuce including 22 simple and 6 mixed or phagedenic chancres; 6 chancres were situated at the urinary meatus or deeply in the canal. In a single instance, the chancre was extragenital (upper lip). Chancre and mucous patches existed in 26 cases. Chancre with roseola was noted in one case.

The secondary eruption was distributed as follows. Erosive syphilides of the glans, one case; buccal erosive syphilides, one case; flat condylomas of the anus, one case, iritis, one case; generalized erythematous or papular syphilides, 9 cases; generalized papular crusty syphilides, fourteen cases; papular erosive syphilides of the scrotum, ten cases; the same with concomitant buccal patches, nine cases; making altogether forty-six cases.

Without entering into a detailed description of the lesions, the statement may be rendered that syphilis in Madagascar although sometimes of very rapid development, passes through the same successive stages as French lues. The secondary stage may be slurred over, but not skipped. It is even the rule for the secondary stage to be rather persistent, but as the symptoms are familiar and not dreaded, while mild manifestations may remain undiscovered, the syphilitic native will seek advice only in unusual and alarming cases; such as extragenital chancres or phagedenic ulcerations. Hence the classical view as to the preponderance of these special manifestations in exotic syphilography.

REPORT OF A CASE OF MULTIPLE CHANCRES ON THE LIPS.—Harry M. Robinson, Baltimore. *Medical Review of Reviews*, 1919, vol. xxv, p. 530.

The report of the following case is of some interest because of the mode of entry of the invading microorganism: M. J., aged 39. Widow. White. Born in Ireland; has been living in America thirty years. Occupation waitress. About eight weeks ago, during

coitus, patient was bitten on the lips, leaving two abrasions on the upper lip and one on the lower. These healed in about two days' time. Two weeks later patient noticed an itching on upper and lower lips, which she rubbed, causing a slight abrasion, which slowly enlarged and became hard. The top became moist and crusted, and when the patient was seen she had three lesions, each about the size of a dime. On the upper lip there were two lesions, one on either side of the mid line. On the lower lip to the mid line was one lesion. The edges were raised, infiltrated and round. The tops of the lesions were covered with a crust moderate in amount, brownish in color; on removal of crust a superficial ulceration was exposed with no exudate. Spirochetes were demonstrated and the Wassermann was positive. One dose of diarsenol 0.4 caused disappearance of lesion.

SYPHILIS OF THE URINARY BLADDER AND URETHRA.—J. T. Windell, Louisville, Ky. Mississippi Valley Medical Journal, 1919, vol. xxvi, p. 251.

H. C., age thirty-seven, married five years, one child, no history of venereal disease. About four weeks before consulting the author he was injured in a ball game, and a week previous to his visit had bladder distress. Many similar attacks had been previously experienced, but none of sufficient severity to cause him to consult a doctor. The urine was cloudy, voided frequently day and night. Albumin 1-10 per cent. Sediment scanty and showed a few pus cells, some epithelium and several varieties of germs, principally *B. coli*. Slight hemorrhage followed each hydrostatic irrigation for about a week. The bladder was then investigated and contained no residual urine. The cystoscope showed a trabeculated bladder. The trigone was red and rough. Healed areas interspersed among large inflamed surfaces were noted. The seminal vesicles were enlarged and very tender, and the expressed material showed under the microscope: nonmotile spermatozoa, leucocytes, epithelium and numerous cocci. Tubercle bacilli were not present in any of the specimens and the von Pirquet test was negative. The deep urethra was the site of chronic inflammation, and the verumontanum bled easily during urethroscopy. The ureters were catheterized with difficulty owing to the fact that the natural landmarks of the base of the bladder were changed by the scar tissue and ulceration. The urine from each kidney was clear. That from the left side showed albumin and a few leucocytes. Several attacks of a severe pain in the left loin necessitated the administration of morphia. These attacks of pain were not frequent, but as they were in many respects similar to those occurring with genito-urinary crises, their occurrence helped to strengthen the chain of evidence that ultimately

formed the suspicion of syphilis as the etiologic factor. Local treatment was of little avail except to restore the urethra to normal and to reduce the congestion of the seminal vesicles. He was circumcised by a general practitioner at the age of twenty-two. About two weeks after this operation he had to consult a surgeon on account of the condition of his penis, which had become infected and swollen to an enormous size. He remembers that after the swelling subsided that there remained five or six indurated areas which we know from subsequent events were initial lesions of syphilis, most likely due to contaminated instruments of the doctor. Six months after his first visit a diagnosis of syphilis was made. Wassermann reaction two-plus. Treatment for syphilis was at once instituted, but owing to the fact that his urine showed about 1-20 per cent of albumin, salvarsan was not administered until six months later.

P. T., age forty-nine, married, one child eighteen years old. Several attacks of hematuria. For more than a week his urine had been bloody. The urine passed in the office was bright red. The centrifuged specimen showed 1-10 per cent of albumin. He had six ounces of residual urine, which varied from that amount to four ounces during the time he was under my care. The cystoscope showed a healthy mucosa except slight engorgement around the left ureteral opening and at the internal meatus. Urethroscopy showed a granular and hemorrhagic verumontanum. Ten days' treatment relieved all the bladder and urethral symptoms except the residual urine. The Wassermann test of the blood gave a one-plus positive. This, in the author's opinion, was a typical case of syphilis of the deep urethra. The patient refused further treatment.

V. J., age fifty-eight, consulted the author during August, 1915. Married and father of several children. Gave a history of having had gonorrhea when a young man. Bladder distress for a long time. The urine was clear, few pus cells in the sediment. No albumin and no residual urine. The deep urethra was very tender. The treatment instituted caused his urine to become clear. He still complained of pain and had to urinate several times during the night. His tongue was sclerosed. He denied syphilis and was indignant when it was suggested. However, he was prevailed on to have a Wassermann, which proved to be four-plus. The cystoscope revealed a trabeculated bladder, scars of healed ulcers, and slight median bar enlargement. The treatment in this case was actively administered; salvarsan, mercury by inunction and intramuscular injection, together with large doses of iodide of potassium. Most of his symptoms have been relieved. The deep urethra still shows evidence of old inflammation, and he has to micturate twice at night.

SYPHILIS OF THE EPIDIDYMIS.—H. E. Michelson, Minneapolis. *Journal of the American Medical Association*, 1919, vol. lxxiii, p. 1431.

Syphilitic involvement of the epididymis is not an extremely rare occurrence, and will be more frequently found, if looked for. Bilateral involvement is unusual. The more common type is the chronic diffuse interstitial type. Some cases of hydrocele are due to syphilis. All patients presenting themselves for disease of the scrotal contents should be examined for syphilis. The diseased portion is not necessarily confined to the upper pole, the entire epididymis being frequently involved.

OCULAR DISTURBANCES AND SYPHILITIC MENINGITIS.—Cosse. *Gazette Medicale du Centre*, 1919, p. 10.

Three patients under the author's observation presented severe ocular disturbances in the course of syphilitic meningitis. There was no doubt about the syphilitic infection in these three cases, and the signs of meningitis manifested themselves especially by ocular disturbances and headache, namely the signs of pachymeningitis localized at the level of the optic chiasm. The ocular lesions involved exclusively the optic nerve, without disturbance of the motor nerves of the eye or other paralytic or sensory manifestations. Whereas the signs of meningitis, aside from the ocular disturbances, were inconsiderable, the eye lesions on the contrary were very severe in all three cases, one of the patients becoming entirely blind. Treatment consisted exclusively of intragluteal or intravenous injections of mercury. In one instance, this treatment acted like a charm, and the patient was completely cured. In another case, the patient's normal vision was restored after a series of twenty intragluteal punctures. In the third case, the treatment remained inefficient, the condition terminating in total and incurable blindness. This particular observation concerned a recurrence at the end of three years, in a man 25 years of age, who developed syphilitic meningitis with compression of the optic chiasm, neuro-papillitis of descending origin, and subsequent atrophy of both optic nerves.

PLEURO-PULMONARY AND MEDIASTINAL SCLEROSIS IN CHILDREN AND CONGENITAL SYPHILIS.—L. Nadal. *Thèse de Paris*, 1919.

The author points out that congenital syphilis, aside from the cases where it gives rise to specific lesions of the lung and mediastinum, also seems to be responsible for the onset of certain pleuro-pulmonary and mediastinal sclerosis in children, an important factor not yet sufficiently recognized. Syphilis may act alone, or

in association with tuberculosis. The pulmonary scleroses met with in congenitally syphilitic children from three to fourteen years of age, involve to a variable degree the pleuræ and lungs; they are invariably accompanied by bronchiectases. The condition of the young patient is often misinterpreted as cavernous tuberculosis, pneumonia, pleurisy, or simple bronchitis. Pleuro-pulmonary sclerosis usually follows upon bronchopneumonia complicating pertussis, measles, or influenza. Mediastinal sclerosis is as a rule of tuberculous origin, but the patient usually has congenital syphilis. Sometimes, syphilis is the only cause. In all youthful patients presenting a tendency toward sclerosis of the lungs, the bronchi, the pleuræ or the mediastinum, congenital syphilis should accordingly be looked for by means of all available methods of investigation. The examination must include a search for dystrophic stigmata, manifest syphilitic lesions of the skin, the mucous membranes and the bones, ocular disturbances, etc. A careful study must be made of the patient's personal history, the direct and collateral heredity, the Wassermann reaction of the blood. Specific treatment alone is to be relied on as efficacious, although this mode of treatment, with mercury or arsenic, can exert no action upon once established sclerotic tissue. When this medication is adopted at a late stage, all it can do is to oppose the further extension of the sclerotic process.

SYPHILIS OF THE MOUTH AND PHARYNX.—Nelson S. Weinberger, Sayre, Pa. *Pennsylvania Medical Journal*, 1919, vol. xxii, p. 804.

In a general way three points present themselves in syphilis of the mouth and pharynx. (1) The mouth and throat are the most common site for secondary and tertiary lesions to appear; (2) excepting when primary, the lesions are a local manifestation of constitutional disease; (3) the treatment is local only when palliation is required in addition to the really important constitutional medication. The primary lesion or chancre is far more common in the mouth and pharynx than is generally believed and often escapes discovery owing to the insignificance of the lesion, undue carelessness on the part of the patient, or the indiscriminate application of local remedies, caustics and even the knife. The lesion is found on the lips, tongue, palate, faucial pillars, tonsils and rarely on the posterior pharyngeal wall. The mucous patch, about which we all hear and read so much and occasionally see, is unfortunately too often looked for to the exclusion of the other equally important lesions. It is simply one of the pathologic forms by which the lesion manifests itself in its variations from erythema to superficial ulceration. It is not a true ulcer but is a result of necrosis of su-

perforial epithelia, is not elevated as commonly taught, and is surrounded by a narrow zone of redness. It is a persistent lesion and is not limited to the secondary stage but often makes its appearance in the tertiary. The chief site is on the soft palate, uvula, and tonsils, but it also occurs on the cheeks, especially opposite an irritating and jagged tooth, the gums, tongue, and inner border of the lips. The tertiary lesions exhibit their ravages in several different ways and as far as time is concerned lesions usually ascribed to the secondary stage may be present in the tertiary. This holds true with scarcely a time limit. The lesions regarded generally as tertiary are diffuse or circumscribed inflammatory infiltration, induration and swelling, gumma formation and superficial and deep ulceration. The tonsils may be entirely destroyed by deep ulceration and necrosis. The necrotic process may involve the hard palate and upper and lower jaw bones. In fact, this destruction may take place in any of the hard or soft tissues about the mouth and throat. The secondary lesions of congenital syphilis in the mouth and pharynx usually appear as erythema or mucous patches during the first few weeks after birth. The tertiary lesions from four to twenty years are the typical gumma and ulceration. These congenital lesions either secondary or tertiary are identically the same as acquired. Hutchinson's teeth are stigmata of congenital syphilis. One of the most difficult problems in differential diagnosis sometimes presents itself in the similarity of some of these syphilitic to tuberculous lesions.

CEREBROSPINAL INVOLVEMENT IN HEREDITARY SYPHILIS.—Philip C. Jeans, St. Louis. *American Journal of Diseases of Children*, 1919, vol. xviii, p. 173.

According to a survey of the literature there is found involvement of the central nervous system, as shown by the cerebrospinal fluid, in about one-third of all individuals with acquired syphilis. Among the 214 patients of this study having hereditary syphilis, a similar incidence of involvement of the central nervous system has been found. The treatment of hereditary neurosyphilis, need differ in no way from that of acquired neurosyphilis, since it can be carried out safely with the same intensity in both instances.

FURTHER OBSERVATIONS ON THE RELATION OF AORTIC INSUFFICIENCY TO THE WASSERMANN TEST.—Julien E. Benjamin, Cincinnati, Ohio, and Sydney J. Havre, Akron, Ohio. *Journal of Laboratory and Clinical Medicine*, 1919, vol. v, p. 47.

A report is hereby made of 33 cases of aortic insufficiency unassociated with any other organic cardiac disease from a clinical standpoint. Wassermann reactions, taken in each case, were posi-

tive in only 11 per cent as against the reported higher rates of other writers. Undisputed histories of rheumatism were obtained in 57 per cent of cases. Questionable histories of rheumatism and histories of frequent attacks of tonsillitis were noted in 15 per cent. A tabulation of results as regards occupation, age, race, and incidence is reported.

APPLICATION AND INTERPRETATION OF THE WASSERMANN TEST AND OF SUPPLEMENTARY LABORATORY PROCEDURES.—Horace Greeley, Brooklyn, N. Y. *New York Medical Journal*, 1919, vol. cx, p. 546.

A patient infected with syphilis does not show a positive complement-fixation test until the organisms have spread widely in his system, so that we readily realize the great evil of purposely delaying final diagnosis and the beginning of treatment, until such confirmation can be obtained. It is usually from two weeks to two months after infection before an untreated person's blood will give a positive complement-fixation test. In the secondary stage all untreated cases of syphilis give positive complement-fixation tests. It should be recollected that the Wassermann test is not for specific substances produced in response to the infection, but rather for antilipoid substances developed as a consequence of the large amount of such waste produced during active syphilis. This is why latent syphilis, including a few cases of congenital syphilis (in which the infection is sometimes inactive) frequently gives doubtful Wassermann tests. In cases where treatment has been given Wassermann tests are positive in proportion to the extent and activity of the remaining infection. In late syphilis with active lesions most authorities have reported that about ninety per cent of the patients show positive complement-fixation tests. Such reports depend, of course, upon the classification of the cases. The value of the luetin test is dependent upon the amount of specific organism there is in the material employed. If this proportion is large, the test can be relied upon to give pathognomonic response in all cases of syphilis in which some degree of resistance (immunity) has developed. While some authors assert that in distinct cases of paresis positive blood complement-fixation tests are obtained to the extent of 100 per cent, it is universally admitted that twenty-five per cent of cases of tabes fail to do so, although giving a positive result when the spinal fluid is examined in at least seventy-five per cent of the cases. Spinal fluids for examination by the Wassermann test should, as in the case of blood, be as fresh as possible, since by keeping even sterile specimens on ice for three or four days, a positive reaction may be missed. The colloidal gold (gold sol) test of the spinal fluid is well known to be of small use

in detecting syphilitic infection, *per se*, yet since it has been found to give almost 100 per cent characteristic reactions (complete precipitation in first 4-8 dilutions) in clinical cases of paresis it is of greatest value when one wishes to decide whether this condition is developing. As the prognosis is most serious in paresis, a positive gold sol reaction of the spinal fluid in a known syphilitic is to be regarded as indicating an unfavorable outcome.

THE TYRANNY OF THE WASSERMANN TEST.—H. Lisser, San Francisco, *Journal of Cutaneous Diseases*, 1919, vol. xxxvii, p. 754.

A strongly or definitely positive Wassermann reaction is undoubted evidence of syphilis. It is an invaluable aid in the diagnosis of syphilis, especially in those cases where physical diagnosis does not reveal positive evidence of the disease. A negative Wassermann means exactly nothing. (a) It does not prove the absence of syphilis, because negative tests occur in cases urgently requiring treatment. (b) Therefore it can not denote a cure in treated cases. A positive Wassermann reaction means syphilis, but not necessarily active syphilis. Once the diagnosis of syphilis (after the primary stage) is established, the patient should be properly treated from two to four years, depending on the stage of the disease and the severity of the lesions. Treatment should be entirely independent of the Wassermann reaction because negative Wassermann reactions occur prematurely during treatment, while positive Wassermann reactions frequently persist long after clinical cure. Once the diagnosis of syphilis is positively established, the fewer Wassermann tests done the better, both for the peace of mind of the patient and the physician. The Wassermann test should be employed as an aid to clinical judgment, but not to supplant clinical common sense.

IMPROVING THE WASSERMANN TEST.—B. W. Rhamy, Fort Wayne, Ind. *Journal of the Indiana State Medical Society*, 1919, vol. xii, p. 207.

In the writer's hands the ice box method always gives stronger reactions by both simple and cholesterin antigens in all positive cases and has shown so far about 10 per cent more positives than the incubator method and is, therefore, just that much more valuable both in diagnosis or in judging a cure. During treatment, however, if the clinician would judge whether the antibodies are decreasing, the incubator figures should be noted, for as will be seen from the foregoing, the incubator results are quantitative, i. e., the strength of the reaction depends on the number of antibodies in the blood while the ice box method of slow incubation (sixteen to twenty-four hours) gives the mass reaction spoken of by Simon. It is safe to say that in the hands of pathologists who have by long

training and experience become thoroughly competent in using all these refinements of technic, the percentage of error in the Wassermann test will be very small indeed and given these conditions there is no process in biochemical diagnosis that will give the clinician more trustworthy information.

THE INFLUENCE OF INCUBATION AND THE CHOICE OF ANTIGENS IN THE WASSERMANN REACTION.—E. D. Hitchcock, U. S. N. R. United States Naval Medical Bulletin, 1919, vol. xiii, p. 740.

Sufficient time must be allowed to complete the fixation of the complement; where few antibodies are present a longer period of incubation is required. This is best accomplished by a period of not less than four hours in the refrigerator. The one-half hour period of incubation is not sufficient and will lead to false negative cases. Twenty-four hours at room temperature fixes the complement completely, but may give false positives and anticomplementary reactions. Cholesterolized antigen is more sensitive than the other antigens and gives a better gauge as to treatment required and progress of case. The alcoholic extract is satisfactory as an antigen where a minimum incubation period of four hours in the refrigerator is used. The acetone insoluble antigen is especially satisfactory and more constant than the alcoholic extract where the period of incubation is one hour or less in the water bath or the incubator at 37° C.

A COMPARATIVE STUDY OF THE ORIGINAL WASSERMANN REACTION AND THE HECHT-WEINBERG-GRADWOHL MODIFICATION.—M. E. Steinberg and Mark Bergeron, U. S. P. West Virginia Medical Journal 1919, vol. xiv, p. 94.

In three hundred duplicate sera examined by the original Wassermann technic and the Hecht-Weinberg-Gradwohl modification the author found that the latter is a very sensitive reaction, giving stronger reactions or a positive reaction when the original may be entirely negative. When the original reaction was entirely negative, 2.6 per cent gave one or two-plus positives by the Hecht-Weinberg-Gradwohl modification. When the original gave one-plus positive, the Hecht-Weinberg-Gradwohl modification gave two and three-plus positives in 1 per cent of the cases. In 3 per cent of cases the original technic gave two-plus and the Hecht-Weinberg-Gradwohl modification three-plus. In all three hundred duplicated sera examined the Hecht-Weinberg-Gradwohl technic gave a stronger reaction or positive reaction in 7 per cent of tests when the original Wassermann was negative or weakly positive. The Hecht-Weinberg-Gradwohl test is not only valuable as a duplicate

test to avoid any discrepancy in the technic of the original reaction, but by means of this reaction an occasional positive reaction may be obtained, when by the original technic the serum is negative.

A PRELIMINARY REPORT ON THE ICE BOX METHOD OF PERFORMING THE WASSERMANN REACTION.—N. Hamilton Fairley and C. F. Sullivan, Australian Army Medical Corps. *Journal of the Royal Army Medical Corps*, 1919, vol. xxxiii, p. 268.

The substitution for the first stage of the Wassermann reaction, of the ice box method (six hours at 8° C.) and the use of the cholesterolized alcoholic heart extract of Fildes and McIntosh affords a superior technic to that usually employed. It is a more reliable method in the diagnosis of syphilitic infection, especially in early primary and late tertiary syphilis. It affords a more accurate index to the cure of the disease. Using the ice box technic as above described there is no increased tendency to pseudopositive reactions either in normal sera, or in the various protozoal diseases investigated. It converts a number of border line cases or partial positive reactions as yielded by the ordinary method into strongly positive reactions.

THE INSTABILITY OF RED BLOOD CELLS PRESERVED IN THE METHOD OF ROUS AND TURNER.—George Dreyer, Oxford, England. *Lancet*, London, 1919, vol. cxcvii, p. 687.

By means of Rous and Turner's method it is not possible to obtain a standard suspension of red cells of constant sensitiveness to hemolysins. Therefore the use of such suspensions as a standard unchanging material for experimental work or for routine complement-fixation tests would necessarily lead to erroneous results.

THE ACTION OF SYPHILIS ON NATIVE COMPLEMENT.—B. H. Shaw, Stafford, England. *British Medical Journal*, July 26, 1919, No. 3056, p. 105.

Syphilitic serum, it is already known, shows, as compared with normal serum, a diminution of complementary activity in varying degrees when incubated with sensitized cells. For example, normal serum showed complete hemolysis when incubated in a water-bath at 37° C. for six minutes (in the proportion of 1 vol. of 1 in 10 serum) with 1 vol. of sensitized cells 3 per cent and 2 vols. of normal saline, whereas a similar amount of syphilitic serum under similar conditions took thirty minutes to bring about complete hemolysis. The specific serum in this instance was from a case of tertiary syphilis. The author has noticed that in cases of early acquired syphilis after successful treatment by salvarsan, etc., and

resulting negative reaction of the "Wassermann" test, the serums are also deficient in complementary activity to a very marked degree. Complementary activity of serum does not diminish so rapidly as is generally thought when the serum is kept under suitable conditions, but this diminution is more rapid in proportion to the degree of positivity of the complement-fixation test, and the return of a serum to normal conditions as regards the "Wassermann" test does not appear to effect any corresponding change in complementary activity. This result is not what would be expected on the supposition that deficient hemolysis is due to the presence of antigenic substances in the serum.

THE "DELAYED NEGATIVE" WASSERMANN REACTION.—Guthrie McConnell, Cleveland, Ohio. *Journal of Laboratory and Clinical Medicine*, 1919, vol. v, p. 43.

It would seem advisable that readings should be taken every fifteen minutes after the hemolytic system has been added and the tubes placed in the incubator or water-bath. By so doing there will be a certain number, about 1 per cent, that will give a so-called "delayed negative" reading. Of these nearly three-fourths will give either a positive or a very suspicious history in regard to venereal infection. Although such reactions are few and far between, very little additional labor is required, and information about the occasional case is frequently important.

THE DIAGNOSIS OF LATE SYPHILIS OF THE CENTRAL NERVOUS SYSTEM.—Channing Frothingham, Boston. *American Journal of the Medical Sciences*, 1919, vol. clviii, p. 312.

It is apparent that in a very high percentage of the cases there are strongly suggestive symptoms in the history or positive signs on the physical examination. It must be borne in mind, however, that many of these cases might have shown an increased cell count and a positive Wassermann test in their spinal fluid long before any symptoms on the part of the central nervous system appeared. These cases, therefore, help us little, if any, in trying to decide if involvement of the central nervous system in old syphilis occurs without physical or other signs. On the other hand, in all the groups of cases except that of syphilitic meningitis there was a small percentage of cases in which there were no signs or symptoms to call one's attention to the central nervous system. These cases, therefore, would have been missed in the routine examination of patients at this hospital but for a custom of investigating the central nervous system in many of the old cases of syphilis discovered on examination or by a routine blood-Wassermann test.

Even more striking in regard to the need of investigating the spinal fluid in cases with positive Wassermann, in which the infection was some years previous, are the two cases in which a positive Wassermann in the blood had been ignored because of lack of symptoms or signs and in which subsequently evidence of advanced tabes was found. This small group of cases shows definitely that it is possible to overlook involvement of the central nervous system with syphilis in an ordinary careful history-taking and physical examination as completed in the wards of a general hospital even when syphilis is known to exist. This possibility of error must become magnified in busy out-patient clinics. The study of the spinal fluid will readily give evidence of syphilis of the central nervous system when symptoms and physical signs are not obtained on careful routine examination. Therefore, as the procedure of lumbar puncture, although somewhat time-consuming to the patient, is practically without danger; and as it opens up a means of diagnosing late syphilis of the central nervous system when other diagnostic means fail, and as late syphilis of the central nervous system calls for special form of treatment, it seems fair to demand that in all cases of old syphilis a lumbar puncture should be performed as a diagnostic procedure before instituting treatment.

A CLINICAL STUDY ON THE USE OF CALOMEL INUNCTIONS.—H. N. Cole and Sidney Littman, Cleveland. *Journal of the American Medical Association*, 1919, vol. lxxiii, p. 1409.

Observations on a series of fifty-four patients treated intensively with calomel rubs show that: 1. Calomel inunctions are almost totally inefficient against primary and secondary syphilis. 2. Calomel inunctions very rarely produce salivation or gingivitis. This means poor absorption of the mercury and explains this clinical inefficiency. 3. Calomel rubs may occasionally produce a dermatitis. These results have led the authors to abandon calomel inunctions, and they would strongly advise against their further use in the treatment of syphilis.

RECENT PROGRESS WITH SYPHILIS.—H. G. Irvine, Minneapolis. *Journal of Cutaneous Diseases*, 1919, vol. xxxvii, p. 702.

In a general way, one might say that there has been a tendency to centralize both the teaching and treating either in a department by itself or, as the writer believes best, in the department of dermatology and syphilology. The advantage of this is of special value in the treatment, in that it places the responsibility squarely up to one department or to one individual as the head of that de-

partment. Perhaps the most practical step in progress resulting from the campaign has been the opening of hundreds of new dispensaries. In May the U. S. Public Health Service reported over 250 dispensaries operating in conjunction with their service. Much is being made of laboratory service, and nearly all states offer, or will shortly offer, free Wassermann tests. This will result in much harm if not expertly controlled, and the profession needs much assistance in being taught to place the proper value on this test.

THE TREATMENT OF SYPHILIS WITH MERCURIALIZED HUMAN SERUM.—
Carl H. Bastron, Lincoln, Nebraska. *Nebraska State Medical Journal*, 1919, vol. iv, p. 230.

The obvious advantages this method has over intramuscular and subcutaneous injections are: Freedom from pain, quicker action, the dosage is absolutely under control; the patients rarely object after the first injection. It has the following advantages over inunctions: It is less objectionable to the patient, acts more quickly, its dosage is under control, and the patient is under closer observation by his physician. A seeming drawback to this as well as other methods of intravenous medication is the occasional difficulty of finding a vein, as in fat subjects, children and negroes. If a vein can not be located in the epitrochlear space, the writer has often succeeded in finding a fairly large vein on the radial side of the wrist by placing the tourniquet just above the wrist. Injections are made with an all-glass luer syringe and a small hypodermic needle. It is preferable to use a very small needle, as it will be less painful to the patient, and the danger of too rapid injection is prevented. Other advantages in using a small needle are that smaller veins can be injected; the needle enters the vein easier, since less force is required to push the needle through the skin, thus preventing slipping of the vein from under the needle; and a small needle is not so apt to lacerate the vein as a large needle. Laceration of a vein may lead to the obliteration of the same, especially if some of the bichlorid mixture has been injected, and it always leads to extravasation of blood and a black and blue mark. In children it is better to use inunctions, although it seems a safe procedure to inject the serum into the longitudinal sinus, making sure the needle is in the sinus. The writer is of the opinion that this is the best, if not ideal, method of treating syphilis in all its stages, the arsphenamine brand of preparations not excepted. Bearing in mind the doubt that still beclouds the intraspinal treatment of syphilis, and the severe reactions that often follow it, and with the slight improvement obtained, the writer does not hesitate to proclaim the method just described as the method par excellence in all stages and types of syphilis. The intravenous injection of

mercurialized serum acts fully as quickly as arsphenamine in clearing up symptoms, and the consensus of opinion of both old and present-day syphilographers places mercury in a unique position in the therapy of syphilis. The method is especially applicable in cases in which quick effects are sought.

THE TECHNIC OF ARSPHENAMINE ADMINISTRATION.—O. LeGrand Suggett, St. Louis. *Southwest Journal of Medicine and Surgery*, 1919, vol. xxvii, p. 170.

The drug must be pure, and of the proper light yellow color; placing the ampoule in a small beaker of alcohol ten minutes before opening will detect any cracks, and if found the ampule should be wholly discarded. The patient should be examined especially for any cardiac, aortic, or renal disease, and be properly prepared. The solution should be alkalized to the minimum degree necessary to clarify it, should be about the color and transparency of normal urine,—the red or reddish brown mixtures, which are opaque or barely translucent, thrown away,—it should be filtered, as often it is not, given at blood temperature or very slightly warmer, and immediately after mixing, as it undergoes rapid changes after exposure to the air. Unquestionably only freshly distilled water should be used, and finally 0.6 gm. may be given in 50 c.c. of water with absolute safety, so far as that feature alone is concerned.

THE MIXING AND ADMINISTRATION OF ARSENICAL PREPARATIONS.—William J. Young, Louisville, Ky. *Mississippi Valley Medical Journal*, 1919, vol. xxvi, p. 286.

The most approved method of giving intravenous salvarsan is by gravity. The syringe method during the last few years has had a wave of popularity and is still being used by those who are willing to persuade the patient to take chances because of its convenience and simplicity. The advantage of the gravity over the syringe method is: (a) a larger dilution of the drug, and (b) a more gradual intake of the solution. If the syringe is used the tendency is to inject the solution within twenty seconds to one minute. It is impossible to gauge the time unless a watch is placed beside the operator or an assistant "calls time," and even then the injection will not be uniform. With the gravity apparatus one can regulate the flow so as to gauge the time according to the amount of the solution to be introduced. To insure the least toxic reaction the time in the author's work is fifteen minutes for a dose of 0.6 gram salvarsan, or 0.9 gram neosalvarsan; 20 c.c. of freshly distilled water to each 0.1 gram of the arsenical preparation injected is the dilution used; and where a smaller dose of salvarsan is given less time would naturally be consumed. In clinic work he uses 10 c.c. to 0.1

gram of salvarsan owing to the number of cases to be treated and the limited time of the clinic. There have been no fatalities in over five thousand doses given during the last year, and he feels justified in continuing the method because of the number of patients it enables us to handle in our limited time.

THE ADMINISTRATION OF CONCENTRATED ARSPHENAMINE AND ITS RELATION TO THE NITROID CRISIS.—Ray S. Morrish, Flint, Michigan. *Journal of the Michigan State Medical Society*, 1919, vol. xviii, 467.

There is still a variance in opinion as to the cause of the nitroid crisis. Recent studies tend to show that it is of chemical origin due to the action of arsphenamine upon the protein content of the blood of certain syphilitics, causing an intravascular precipitate either of the drug, or of the colloids of the blood plasma. The rapid injection of a concentrated solution of arsphenamine, properly alkalized, is apparently not a causal factor in the production of the nitroid crisis. It affords a safe and convenient method for the treatment of a large number of patients in a relatively short period of time. The results obtained by this method compare favorably with other methods in the proportion of crises observed. Adrenalin is an apparently satisfactory therapeutic agent. Its greatest use would seem to be in its employment as a prophylactic measure, rather than as a means of cure. It may be used intravenously with arsphenamine.

THE ADMINISTRATION OF ARSPHENAMINE.—Albert S. Hyman, Boston. *Boston Medical and Surgical Journal*, 1919 vol. clxxxi, p. 353.

The author has found it convenient to divide the reactions into four general clinical groups, depending in some part upon the time of their manifestation after the reception of the drug. The first group shows an immediate reaction to the intravenous injection of the solution and is indicated by an increasing congestion of the blood vessels of the face and neck. The patient becomes cyanotic and complains bitterly of a peculiar oppressive sensation in the chest, particularly under the sternum. The congestion is sometimes tremendous and startling; the dyspnea increases, and the patient cries out as though in agonizing fear. In a few minutes, however, the congestion gradually subsides, the respirations are easier, and the patient is apparently none the worse for his "ordeal," and ordeal it is, for usually the patient will refuse subsequent intravenous treatments because of their apprehensive character. This immediate type of reaction occurred in about 1 per cent of his cases; the patients were men and women of the so-called "plethoric disposition" type. The second type of reaction which may follow

the use of arsphenamine develops within the first twenty-four hours after the reception of the drug. It may start within twenty minutes but the majority of our cases have occurred from three to eight hours after the injection. The patients present nausea of varying severity, vomiting, severe throbbing frontal headache, hyperpyrexia, occasionally severe abdominal pains, and pains throughout the bones and joints. A sudden diarrhea is common. The urine is usually increased in volume and has a specific gravity which is higher than its volume would indicate; traces of albumin and a few casts are commonly found, but of great significance is its reaction, which is, almost invariably alkaline. The symptoms increase in severity for about two to six hours and then gradually clear up, leaving the patient weakened but not seriously affected. This is the most common reaction following the use of arsphenamine and its occurrence has been recorded by many observers. The author had 48 such cases, representing about 9.6 per cent reaction; in other words, one person in ten will react in this fashion. The third type of reaction is not common; in his series he had three cases, or 0.6 per cent. It is shown by those patients who present an alleged idiosyncrasy or intolerance toward the arsenical compounds. This reaction has been described as a subacute or delayed arsenic poisoning which develops a well-known clinical picture. Several days, or possibly weeks, after an injection of arsphenamine the patient begins to grow gradually weaker, the appetite is lost, vague and shifting pains are complained of; a severe diarrhea, occasionally constipation, occurs. The patient suffers from an increasing gastritis, with uncontrollable nausea and vomiting. Hematemesis is not uncommon in severe cases. The liver dullness is said to decrease, although our cases have not shown this feature. There may be jaundice. The urine is usually scanty, high colored, with traces of albumin and hyalin casts. Bile and blood cells are found. One occasionally finds traces of sugar. The fourth type of reaction, the so-called Herxheimer reaction, he has seen in only one of his cases, due, perhaps to the fact that his clinic consists of young adults, and few of his patients are over 50 years of age. The one case referred to was a tabetic of 58 who presented alarming cerebral symptoms for four days, and then cleared up. The author's technique and apparatus are minutely described.

REACTIONS FOLLOWING THE ADMINISTRATION OF ARSPHENAMIN.—William H. Guy, Pittsburgh. *Journal of the American Medical Association*, 1919, vol. lxxiii, p. 901.

There may be included in the group of reactions due to technical errors those that developed in men that either disregarded instructions regarding preparation or were injected without preparation in special instances, as in early primary lesions in which the diag-

nosis had been made by the dark field method. Of the latter, eight of approximately 150 vomited within an hour after receiving a full therapeutic dose of the drug. Nothing further was noted except nausea preliminary to emptying the stomach, and later injections were without reaction, including twenty-five cases in which injections were given on each of three successive days after the method of Pollitzer. On one occasion, when a new lot of salvarsan (Metz) was used, thirty-five severe reactions developed in thirty-five patients injected. Each had a severe chill from forty minutes to an hour after injection, the chill in some cases lasting as long as two hours. Of particular interest has been a group of about forty cases in which reactions developed that could be shown to be due to an aggravation of a nonsyphilitic pathologic condition. For instance, several men who had a few bronchial rales at the preliminary examination developed a moderate chill, cough, and generally a rather severe aggravation of mild bronchitis. One of the patients, recently an influenza victim, developed bronchopneumonia in the same manner. Patients with yellow sclera developed a marked icterus in only three of many similar cases. There were two with an aggravation of previously noted urinary findings following the cautious exhibition of the drug. Most patients with evident mild chronic interstitial nephritis tolerated the drug well. Contrary to what we expected, no unfavorable results were noted in five proved cases of pulmonary tuberculosis. There were two cases with early reactions in which the author was forced to the conclusion that a drug idiosyncrasy existed. In one case an alarming train of symptoms developed after each injection of the drug. About three hours after receiving arsphenamine this patient developed a chill, vomited, and was quite prostrated. His heart action became weak and irregular. His symptoms persisted from forty-eight to seventy-two hours, even with comparatively small doses of the drug. Epinephrin did not seem to be of any use. Finally, a mild dermatitis appeared on the forearms, and further injections were temporarily discontinued. After a period of about four months, following the suggestion of Stokes, a preliminary hypodermic injection of $\frac{1}{50}$ grain of atropin sulphate was given and 0.3 gm. of arsphenamine injected without any reaction whatever. Unfortunately this man was released, and further data on the case are not available. In the case of the other patient, with practically identical symptoms, but milder, we were able to administer arsphenamine, by giving 0.1 gm. as a preliminary injection, and following that with the rest of the injection in an hour. The author has found it to be advantageous to inject the drug very slowly in these cases. Of Herxheimer reactions the author has seen only a few. One man with mucous patches developed a severe glossitis following the injection of 0.4 gm. of the drug. Two showed marked aggravation

of throat ulceration following the 0.3 gm. preliminary dose recommended by the War Department. In another case, mucous patches became confluent, and with extension of the larynx produced a complete aphonia which persisted for several weeks. It is his opinion that Herxheimer reactions are the result of the stimulating activity of nonsterilizing doses of arsphenamine, and that they may be avoided by full therapeutic dosage. There have been two fatalities that may be ascribed in any way to antisyphilitic treatment in this series. Approximately 3,000 patients have been treated, some for a short time on account of transfer of station, and others over considerable periods. In one case, after two 0.4 gm. injections four days apart, the patient developed an acute dilatation of the stomach, death occurring on the ninth day. Necropsy revealed nothing of interest except that arsenic could not be found in any of the viscera. This patient had taken arsphenamine before without reaction according to his statement, and so, since this was only one of a group of 165 injected the same day, we feel that this case must represent one of an unsuspected underlying pathologic condition or one of drug idiosyncrasy. The other case was that of a soldier much overweight, but otherwise as far as we were able to determine, quite normal. He received 0.6 gm. of arsphenamine, and after a seven day interval another of the same size. He also received two injections of 1 grain each of mercuric salicylate. According to routine, the urine was examined before each injection of arsphenamine, and found normal. On the third day following his last injection of arsphenamine, he reported to his regimental surgeon for mercury. At that time he stated that he felt quite well except for some local tenderness in the buttock following the previous injection of mercury. The urine was not examined. He was given 1 grain of mercury, and the next morning was found unconscious in bed. A catheterized specimen of urine which revealed almost a solid coagulum of albumin was loaded with blood and granular casts. He died the same day and at necropsy we found an acute diffuse hemorrhagic nephritis. Thus we may again point out the necessity of routine examination of urine before each injection of either arsphenamine or mercury.

A CASE OF "606" DERMATITIS TREATED WITH INTRAMINE.—A. R. Fraser, Aberdeen, Scotland. *Lancet*, London, 1919, vol. excvii, p. 480.

It is extremely difficult to suggest any definite cause for this extraordinary process of tumor formation. Pyemic abscesses containing definite pus occur in severe cases of "606" dermatitis. Here, however, the absence of pus and the sterility of the tumor contents, together with the noninflammatory nature of the swelling, makes it extremely difficult to draw any analogy. The process

seemed to be of the nature of a subcutaneous myxomatous degeneration. In all probability salvarsan was the exciting cause. There seems nothing to suggest that the intramine was in any way responsible for the condition. On the contrary, the author thinks this drug was beneficial, and essentially nontoxic. The immediate improvement following the administration of intramine was very marked. The fall of temperature, the early exfoliation and the appreciable improvement in the general condition coincided with the first and second intramine injections. In spite of the patient's very poor cachectic conditions its intramuscular administration caused no pain or discomfort whatever. Although no such condition has been described, it seems a possible suggestion that his syphilis was in itself the exciting cause. One feels, however, that this is unlikely, since his disease had reached a "latent" condition. It is extremely probable that in both "606" jaundice and dermatitis the benzene or amino group, and not the arsenic, is the causative agent, and as this condition has never been observed as caused by arsenic apart from this chemical combination, the amino radical may also in this case have been the causative agent.

EXFOLIATIVE DERMATITIS, COMPLICATED WITH CELLULITIS, OBLITERATIVE ARTERITIS AND GANGRENE OF TOES, DUE TO ARSPHENAMINE (?).—Henry A. Jones, Howard, R. I. *Journal of the American Medical Association*, 1919, vol. lxxiii, p. 1359.

In the case herewith recorded, the process was fairly rapid and the destruction of tissue complete. In those cases of obliterative arteritis that are mentioned by various authors, larger vessels are as a rule affected. The author was inclined to believe this condition might have been due to syphilis, but in the discussion that followed the presentation of this case to the clinic, the opinion was given that the obliterative process was caused by the lodgment of arsenic in the circulation and tissues, also the last Wassermann test of the patient, which was made April 6, 1919, gave a negative reaction. This would lead us to the supposition that the cause was not syphilitic, but a case of arsenical deposition in the system.

GANGRENE FOLLOWING AN INJECTION OF ARSPHENAMINE.—L. A. Suter, Wichita, Kansas. *Journal of the American Medical Association*, 1919, vol. lxxiii, p. 1611.

The amount of solution used was about 250 c.c. and was given by the three-way cock method with a 10 c.c. syringe. First the syringe was filled with physiologic sodium chloride solution and the needle filled and inserted into the vein. The blood flowed freely into the syringe, the salt solution basin was set aside, and the arspenamine

substituted in its place. The syringe was filled by means of the three-way cock with the arsphenamine solution and the solution injected into the vein. This process was repeated until the 250 c.c. solution of arsphenamine had been given. The vein was entered by the needle at the first attempt. The patient complained of a severe pain in his hand at the time. In a few minutes after the injection his hand was white and death-like cold. He complained of anesthesia and inability to move the hand, and there was a decided wrist drop. Three hours later there was tonic contraction of all the fingers and the wrist. The peripheral circulation was poor. The hand was cold all the time. The next day the tonic contracture was somewhat less, and from that time until two weeks later, at which time he left the hospital, there was very little feeling in the hand. It was apparent that his fingers were becoming gangrenous. About twenty minutes were consumed in giving the injection. Within two hours after the injection his arm began to swell around the needle hole, the swelling extending down over the forearm and up over the biceps muscle. Hot applications were applied to the arm. These were used continuously for two days, after which warm alcoholic dressings were kept on the arm for forty-eight hours. The left arm was carried at an angle of 45 degrees. It could be flexed until the hand was within 6 inches of the shoulder. This caused him considerable pain, however. The forearm could be extended to within 15 degrees of a straight line. The back of the left hand and forearm were covered with large blisters. There were also blisters over the dorsal surface of the fingers and thumb. The cutaneous covering had been removed from the blisters of the back of the hand, leaving a large oozing surface. All the nails were black. The thumb was black for 5 mm. on the palmar surface. The gangrenous area extended through to the nail. There was also a black ring extending around the thumb over the last joint. The skin over all the gangrenous area was extremely shriveled, dry and hard. The index finger was dead and shrunken from the middle phalangeal joint. The middle finger was also dead, black and shrunken within 5 mm. of the middle phalangeal joint. The ring finger had a well marked line of gangrene midway between the second and third phalangeal joint. About one-half of the last phalangeal joint of both little finger and thumb were gangrenous. There were a number of blisters over the tops of the fingers and thumbs, each containing quite a little pus. The muscles of the forearm were very hard, and the entire cutaneous covering of the forearm and hand, excepting where raw areas were, was shrunken, hard and thick. There was very slight sensation for hot and cold over the hand and fingers and very little pain sensation on being stuck with a pin. The wrist could be moved slightly. September 11, under ether anesthesia, the author amputated the thumb slightly

distal to the end of the last phalanx. The index finger was amputated 1 cm. proximal to the middle phalangeal joint. The middle finger was disarticulated at the middle phalangeal joint. Owing to the desire to save as much of the fingers as possible, the ring finger was amputated 1 cm. distal to the middle phalangeal joint. Five mm. of tissue were removed from the end of the little finger. The wound healed in a surprisingly kind manner. At this time there is increased motion of the elbow joint, the wrist and some of the finger stumps. Sensation has greatly improved. The oozing areas of the hand are entirely healed.

A DEATH FOLLOWING ARSPHENAMINE.—A. Goetsch, U. S. Navy.
United States Naval Medical Bulletin, 1919, vol. xiii, p. 797.

It is well known that early syphilis may produce a distinct nephritis of the "vascular type" with or without laboratory findings in the urine. During life it is difficult to estimate to what extent syphilis may interfere with arsenic elimination from the kidneys, particularly in the absence of urinary findings. It is likely, therefore, that arsenical poisoning with production of nephritis may occur as an accumulative effect, in some instances following a second injection of an arsenical when there has been retention of arsenic following the initial injection. The organic compounds of arsenic contain the metal in the nonionic form, and the effects differ materially from those of arsenic in the ionic form partly because the organic molecule acts as a whole and partly, perhaps, because the organic substances alter the selective action of the arsenic and hence prohibit its penetration in effective concentration. Briefly, it might be stated that the difference between organic arsenic and inorganic arsenic is quantitative rather than qualitative. Incidentally, it is difficult to estimate to what extent and how rapidly organic arsenic is changed into the vastly more toxic, ionized pentavalent and trivalent inorganic arsenicals under certain conditions of altered metabolism. Obviously, the extent of these changes can not be determined quantitatively. The cause of death in the case reported was quite obviously acute hemorrhagic nephritis, due to acute arsenical poisoning.

THE COMPARATIVE VALUE OF NOVARSENOBILLON BY THE INTRAVENOUS AND INTRAMUSCULAR METHODS.—L. G. Leonard, R. A. M. C.
British Medical Journal, August 30, 1919, No. 3061, p. 266.

The conclusions reached from the facts set out in this article are: 1. The excellent result of intramuscular novarsenobillon clinically; there is, therefore, scope for the discovery of a combination which will render it painless. 2. The best means for preventing the spread of venereal disease at the present time lies in early

diagnosis and early treatment, and, as regards the army, periodical "short arm" inspection of troops, as at present carried out. This, of course, can not be applied to the civil population. 3. Quackery—advertised "remedies" and counter prescribing—should be more rigorously dealt with in order to prevent serious delay in commencing proper treatment.

ARSPHENAMINE IN PNEUMONIA WITH DELAYED RESOLUTION IN SYPHILITIC SOLDIERS.—George Douglas Head, Minneapolis, and John L. Seabloom, Red Oak, Iowa. *Journal of the American Medical Association*, 1919, vol. lxxiii, p. 1344.

The authors are fully aware of the fact that both lobar pneumonia and bronchopneumonia are self-limited diseases, that resolution of the lung takes place under serocellular processes the nature of which is not known, and that the resolution so promptly brought about in the cases here recited may be explained on the grounds of a natural termination of the disease rather than the arsphenamine effects. However, the impression received in watching from day to day the physical signs and clinical manifestations in these three stubborn cases of unresolved pneumonia in syphilitic soldiers has fully convinced us that the arsphenamine had a specific effect in clearing the lungs, and we advise its use in cases of unresolved pneumonia in syphilitic subjects.

THERAPY OF NEUROSYPHILIS JUDGED BY ARSENIC PENETRATION OF MENINGES.—H. C. Mehrtens and C. G. MacArthur, San Francisco. *Archives of Neurology and Psychiatry*, 1919, vol. ii, p. 369.

Irritation of the meninges by intradural injection of the patient's own serum caused a cellular reaction ranging from 100 to 2,300 cells per cubic millimeter of spinal fluid. Simple intravenous injection of 0.6 gm. arsphenamine resulted in a positive test for arsenic in the spinal fluid in 43 per cent of the cases. Complete drainage of the spinal fluid did not increase the number of arsenic penetrations. Intravenous injection of arsphenamine six hours after meningeal irritation gave 92 per cent penetrations and compared with the controls, gave three times as strong an average concentration of arsenic.

THE TREATMENT OF SYPHILIS AND THE WASSERMANN REACTION THEREAFTER.—E. E. Waters, Howrah, India. *Indian Medical Gazette*, vol. liv, p. 290.

The author has treated over 50 constables in the last eighteen months, and allowing for transfers, leave, still under treatment, etc.,

30 men have had a full course of novarsenobillon and mercury and have had their blood examined twice, sometimes three times, at the serological laboratory after conclusion of treatment. His standard course of treatment has been six injections of novarsenobillon (two each .45, .6, .9 gram), or six of Galyl .3 gram, followed by four to six weeks of inunction with mercurial ointment, six weeks' rest, then a blood examination. Yet with all this treatment, 75 per cent of the cases are no better serologically than they were at the beginning of the course. Clinically, the improvement is enormous; rashes disappear, aches and pains (chronic rheumatism?) vanish, secondary stigmata clear up, and the patients put on weight. Particularly is this the case in nervous and myelitis cases; in these, very marked improvement occurs. Curiously enough, the use of autogenous arsenicalized serum seems to rapidly render the cerebrospinal fluid free from treponemata in syphilis of the nervous system, very much more quickly than vigorous treatment will do the same for the blood stream.

THE USE OF HIGH FREQUENCY ELECTRICAL CURRENTS (DIATHERMY AND AUTOCONDENSATION OF D'ARSONVAL) AS AN ADJUNCT IN THE TREATMENT OF SYPHILIS.—Edward C. Titus, and Frederic DeKraft, New York. *American Journal of Electrotherapeutics and Radiology*, 1919, vol. xxxvii, p. 31.

Electric light, either the high power incandescent lamp or the arc light, may be employed. The mercury-vapor arc light, particularly the quartz lamp, may be used as an adjuvant to other treatment. This is especially useful in old syphilitic ulcers. The good effect obtained from this measure is probably due to the active hyperemia induced by the ultraviolet radiations. This active arterial hyperemia increased the nutrition of the cells affected, and in this way enhanced the resistance to the invading spirochetes in the parts involved. It is not necessary to assume that the ultraviolet radiations have a direct lethal effect on the spirochetes in order to explain the results attained. The static brush discharge from a powerful static machine (obtainable by means either of a wooden stick properly moistened or by means of the asbestos electrode known as the DeKraft blue-pencil electrode) is not only rich in ultraviolet radiations, but furnishes, in addition, electrical discharges which are capable of inducing a proper degree of hyperemia to meet all necessary indications. The Titus electrode attached to the terminal of the Oudin resonator of a coil or transmitter fulfills a similar purpose, or the glass vacuum electrode attached to the Oudin may be used. The x-ray from a high vacuum tube may also serve to stimulate the cells to renewed activity. Diathermy consists of the strictly local application of the direct d'Arsonval current by means of a pair (or more) of metallic elec-

trodes. The material of which these electrodes is made is soft sheet metal. The author prefers pure block tin. This is flexible enough to admit of an even application and good close contact. It can be cut with a pair of shears to suit the individual case. It is usually best to have the number of square inches of the electrodes attached to opposite sides of the solenoid, as nearly equal as possible. To each electrode is attached a clamp as securely as possible, and to this clamp is fastened the conducting cord leading to the apparatus. It is very important that all these connections be firm. If they should become loosened in any way while a current of heavy amperage is passing, our patient would be subjected to a violent shock. The electrodes must be applied in such a manner that the current can find its way directly through the part to be treated. In all diathermic applications it should be a rule never to start with a heavy current. Begin with a little current, 300 or 400 milliamperes, according to the size of the electrodes. Allow the current to find its way and then little by little add to the amperage. Never be in a hurry in any of your diathermic work. Patience and good judgment are admirable qualities here. Syphilitic deafness seems to be peculiarly resistant to treatment. Facial paralysis is frequently due to syphilis and responds well when diathermy is added to other remedies. Diathermy, the effluve from a Titus electrode attached to the Oudin of a transformer and the application of the glass vacuum electrode, each finds a very important field of usefulness in the treatment of locomotor ataxia.

THE TREATMENT OF GONORRHEA AND SYPHILIS IN WOMEN.—William E. Stevens and Maurice Heppner, San Francisco. California State Journal of Medicine, 1919, vol. xvii, p. 287.

Arsphenamine is administered intravenously at intervals of one week together with either inunctions of mercury ointment, weekly intramuscular injections of mercury salicylate with quinine and urea hydrochloride or intravenous injections of mercury bichlorid. Potassium iodide is given in graduated doses by mouth. Mercury inunctions are used at the beginning of treatment as these may be discontinued at the first evidence of an idiosyncrasy on the part of the patient, whereas it is impossible to withdraw anything that has once been injected. For intramuscular injection mercury salicylate with quinine and urea hydrochloride has been found satisfactory and is less painful than other preparations. Mercury bichlorid which may be administered intravenously in doses of one-twentieth to one-sixth of a grain possesses the advantage of accuracy of dosage in addition to freedom from pain and the subsequent disability which sometimes follows intramuscular administration.

THE TREATMENT AND STUDY OF TWELVE NON-PARETIC NEUROSYPHILITICS TREATED BY INTRAVENTRICULAR INJECTIONS OF SALVARSANIZED SERUM.—A. L. Skoog, Kansas City, and Karl A. Menninger, Topeka, Kansas. *Journal of Nervous and Mental Disease*, 1919, vol. 1, p. 114.

Twelve cases of nonparetic neurosyphilis were treated intensively by the intracerebral injection of salvarsanized serum. The technic of the method of treatment used is described in detail. Serum salvarsanized in vivo was exclusively used. Local anesthesia is utilized for trephining; and the parietal area is selected. The reactions to treatment were as a rule not severe, but occasionally became quite alarming and even fatal. The symptoms consist usually in slight febrile reaction, more or less headache, and variously located pains sometimes accompanied by a toxic meningitis of short duration. The twelve cases presented embrace 4 cases diagnosed vascular type of cerebral syphilis, 2 tabes dorsalis, 1 idiot, and 5 cases of unclassified neurosyphilis, 2 of which may be taboparesis. The clinical results of treatment showed marked improvement in 2 cases, slight improvement in 6, none at all in 2, and fatality in 2 cases. The improvement showed no tendency to follow diagnostic classes. The laboratory returns showed as a result of the treatments: (a) Wassermann changed in blood serum in 50 per cent cases, spinal fluid in 50 per cent cases, cerebral fluid in 80 per cent cases. (b) Gold sol in reaction (spinal fluid) diminished in 40 per cent, intensified in 30 per cent. (Irregular in cerebral fluids.) (c) Globulin in cell counts of spinal fluid not markedly altered. The laboratory data indicated marked improvement in 2 cases, slight improvement in 5; none at all in 3. The clinical and laboratory data in point of response to treatment would appear similar numerically: but a study of individual cases shows that they agree precisely on only 20 per cent of cases; and differ completely in 50 per cent, showing a tendency to be reciprocal. It is apparent from the differences in the spinal and cerebral fluids that at least in certain pathologic conditions, such as those presented, there is an interference in the communication channels between the ventricles and the fluid spaces of the spinal cord. Two cases died: one probably as a direct result of the treatment; the other possibly as an indirect result. On the whole, the brief but intensive treatment appears to have given encouraging results, which possibly would have been much more gratifying had it been longer continued. The improvements were moderate rather than extreme, but no cases were made worse save the two who succumbed, either from the laboratory or clinical standpoint. Two cases with rather remarkable improvements are included. One gratifying feature is the enthusiasm with which most of the patients cooperate in and appreciate the

treatments. This is in one way a drawback, as they are apt to consider themselves so much improved that further treatment is unnecessary.

TYPES OF SYPHILITIC DISEASE TREATED AT A PUBLIC CLINIC.—John F. Martin, Boston. *Boston Medical and Surgical Journal* 1919, vol. clxxxi, p. 582.

In the acquired form of the disease, the type that is the most agreeable to treat is the primary stage of the infection, because it is in these cases that the most prompt results of treatment are obtained. A number of discharged soldiers, contracting the disease through venery with diseased panderers, have come to the clinic for treatment during the period of demobilization, all manifesting florescent primary lesions, accompanied by positive Wassermann blood tests. Without exception, under intensive treatment with arsphenamine and mercury, they all showed negative Wassermann blood tests after receiving from six to ten intravenous injections of arsphenamine, two each week, and one intramuscular injection of mercury salicylate a week. The secondary erythematous and papular eruptions are usually amenable to treatment, rapidly fading away, as a rule, and the success in obtaining a negative Wassermann blood test depends upon the degree of tissue invasion, the virulence of the infection, the accessibility of arsphenamine and mercury in reaching the spirochetes, and the resistance of the individual. When the disease has progressed to present secondary symptoms, the cerebrospinal system must be ruled Wassermann negative before one can be certain that a cure has been obtained, even though the individual has repeated negative Wassermann blood tests. The chronic, tertiary types of infection are present in large numbers, human evidence that many escape in receiving benefit of a thorough course of treatment, through some circumstances or other; it might have been their habits or neglect of treatment that hindered their cure, or insufficient treatment, lack of combating resistance or virulence of the disease. As the treatment of syphilis progresses such sequences will become fewer, through the more thorough treatment of the disease in the earlier stages. The neurologic types of syphilitic disease represent the end-journey of the spirochete, and present the parietic, the tabetic, the epileptic, and those with combined, system, segmental, or focal degenerations; also the pre-degenerative or toxic types suffering from neurasthenia, headaches, spasms, neuralgia, and other irritative symptoms of syphilitic poisoning. They all receive their share of attention, and, like the age-worn ship that is made fit for service, all that is possible is done for them to ward off or delay the final day.

THE OVER-TREATMENT OF NEUROSYPHILIS.—D. W. Roberts, Milwaukee. Wisconsin Medical Journal, 1919, vol. xviii, p. 54.

The treatment of neurosyphilis is indeed an individual problem and every case is a law unto itself and must be studied as such. The sooner the spinal puncture in the spirochetic septicemia stage of syphilis is made, the more cases of neurosyphilis will be found and treatment instituted at a period when therapy will produce the most satisfactory results. Neurosyphilitics must have their lives planned so as to maintain the greatest possible defensive body power. They must, when under treatment, be subjected to hospital routine or at least be taken away from ordinary duties. During this series of treatments, every assistance that would build up the general health, such as nutritive diet, pleasant and congenial surrounding, tonic baths and massage, are of the greatest advantage if accessible. Especially the vapor baths seem to permit the patient to absorb more mercury and tolerate more arsphenamine than when otherwise treated. The intravenous administration of arsphenamine in neurosyphilis is of major importance, and should only be given by skilled operators with hospital facilities. The patient should have twelve hours rest in bed, no diet for six hours and a clean intestinal tract. Also he must remain in bed for twenty-four hours after treatment. Not more than four treatments should be given in a series. One series of treatments should last about three weeks, and not more than two should be given in the same year unless the infection be active, then more if patient be in good physical condition. One spinal puncture during each series at the end of second week; this is for laboratory test and spinal drainage.

CEREBROSPINAL SYPHILIS WITH SPECIAL RELATION TO THE OPTIC NERVES.—Mark A. Schoenberg, New York. New York Medical Journal, 1919, vol. cx, p. 452.

Every patient with a primary lesion should have, in addition to a careful general and neurologic examination, a routine ophthalmologic examination. This examination should be repeated at regular intervals during the secondary and tertiary stages. The pupils, the nerves directing the mobility of the eyes and the optic nerves are frequently affected during the early stages of syphilis and indicate the invasion of the central nervous system. The general practitioner can acquire the necessary knowledge for a careful eye examination in a very short time. During the past years the author has seen a number of patients with optic atrophies of various kinds and types. Some of these patients, which he would have regarded before as doomed to complete blindness, have had the process arrested by general and spinal treatment, and others have improved. Their treatment consisted of the usual medication

with mercury, iodide, and salvarsan. In those patients who continue to fail in spite of the general and spinal treatment he made intracranial injections of salvarsanized serum. The work on intracranial therapy is a chapter in itself. There is yet a great deal of preliminary work to be done before we can reach any conclusion on this subject. But regarding the spinal therapy he is certain, from what he has learned from his own experience with certain types of optic atrophies, that it offers us better results than the general treatment alone. Regarding the results obtained in the treatment of these patients with syphilitic optic nerve lesions, one thing is certain, they are relatively good if treated early, during the secondary stage of lues; they are not very bad if we treat them properly, even in the tertiary stage at the earliest appearance of the process, but the results are very poor if the patients come with an old process in the completed atrophic stage. The optic nerves, as much, or even more than the other cranial nerves, must be watched in every luetic patient throughout his entire life. Prompt diagnosis of an involvement of the optic pathways means prompt treatment, and often prevention of blindness.

THE "DELAYED NEGATIVE" WASSERMANN REACTION.—Guthrie McConnell, Major M. C., U. S. Army. *The Journal of Laboratory and Clinical Medicine*, 1919, vol. v, p. 43.

In the course of routine Wassermann examinations it was noted that every now and then there would be a specimen of blood that up to a half hour after having had the hemolytic system added and being placed in the incubator would remain as a strongly positive reaction. Very shortly after that time the blood would very quickly hemolyze and well before an hour had passed would show no traces of unhemolyzed cells.

During the months of February, March, and April, 1793 Wassermann tests were made and of that number there were 18 that were considered "delayed negatives." In this report by delayed negative is understood one in which the tube containing the cholesterinized antigen showed no hemolysis at the end of thirty minutes, but had completely cleared by the time of the following examination fifteen minutes later.

In the hope of coming to some definite conclusion the 18 delayed negatives were studied as carefully as possible. It was found that they can be placed in one of three classes. First, those that give a frank history of syphilis, either of long standing and little treatment, or of more recent infection with treatment. Second, those that might be considered as questionable on account of their generally loose sexual relations. Third, those in whom there can be ob-

tained no history of venereal infection, and who give no clinical symptoms.

Of the eight in class one, seven of them had had antisyphilitic treatment. The eighth case had syphilis eight years ago, but no information relative to treatment was obtainable.

In Class II, all denied having had syphilis, but each man had or had had gonorrhea.

In Class III are four cases, one of these was a man who was a chronic alcoholic. A second case, who denied infection, had been in the ward for a week suffering from acute cholangitis. Of the other two, one had been admitted for lobar pneumonia and one for influenza.

In regard to the frequency of delayed negatives, 1 per cent of all Wassermanns is what is indicated by these figures. Of the total number, approximately 0.44 per cent give a definite history of syphilitic infection, 0.33 per cent were probably syphilitic, leaving 0.23 per cent as probably negative.

To briefly summarize it would seem advisable that readings should be taken every fifteen minutes after the hemolytic system had been added and the tubes placed in the incubator or water-bath. By so doing there will be a certain number, about 1 per cent, that will give a so-called "delayed negative" reading. Of these nearly three-fourths will give either a positive or a very suspicious history in regard to venereal infection. Although such reactions are few and far between, very little additional labor is required, and information about the occasional case is frequently important.

FURTHER OBSERVATION ON THE RELATION OF AORTIC INSUFFICIENCY TO THE WASSERMANN TEST.—Julien E. Benjamin, Capt. M. C., (Cincinnati, Ohio), and Sydney J. Havre, 1st. Lieut. M. C., (Akron, Ohio), Camp Funston, Kansas. *Journal of Laboratory and Clinical Medicine*, 1919, vol. v, p. 47.

A report is made of 33 cases of aortic insufficiency unassociated with any other organic cardiac disease from a clinical standpoint.

Wassermann reactions, taken in each case, were positive in only 11 per cent as against the reported higher rates of other writers.

Undisputed histories of rheumatism were obtained in 57 per cent of cases. Questionable histories of rheumatism and histories of frequent attacks of tonsillitis were noted in 15 per cent.

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SOME OBSERVATIONS ON SYPHILIS OF THE CENTRAL NERVOUS SYSTEM*

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THE aim set for attainment by every medical man should be that any individual coming to him for treatment may be enabled to reach a fairly old age, with the minimum of suffering and misery, may be enabled to carry out his business to a successful conclusion, and may be able to marry and to raise healthy children. In the treatment of few diseases is the importance of attempting to accomplish this aim as necessary as in the treatment of syphilis and particularly that form of syphilis which attacks the central nervous system. Neurosyphilis, if unchecked, is one of the most disastrous of diseases. Although only about 20 per cent of syphilitics develop neurosyphilis, when this percentage is computed on the syphilized population of a country it makes the question not only an individual one but one of the greatest importance to the State. The nature

*Report from the Syphilitic Clinic of the Canadian Special Hospital, Etchinghill, Lymeing, Kent, England.

of the disease itself, with its insidious development during which time the patient feels absolutely well, its onset during the prime of life, the misery and suffering endured both by the patient and his friends, the loss of power to earn a livelihood and the eventuality of his becoming a charge on the State until a miserable death from paresis or tabes ensues, make an early diagnosis and early and efficient treatment of the utmost importance. Early diagnosis and the early institution of treatment are necessarily of extreme importance, for the unfortunate part of the disease is that when symptoms commence to manifest themselves unregenerable neurones are already destroyed so that treatment, if then adopted, may be sufficient to check the disease but can not reconstruct the obliterated nervous pathways. The amount of neurosyphilis in a population varies directly with the number of cases of syphilis undiagnosed and insufficiently treated, the number in which treatment has been delayed, and the number of cases of neurosyphilis in which the physician in charge of the case is unfamiliar with modern methods of treatment. If every case of syphilis was treated thoroughly and sufficiently over a proper time period, treatment being commenced before the signs of generalization appear and before the Wassermann has become positive in the blood, syphilis of the central nervous system would be almost unknown. It can not be too strongly impressed upon the general practitioner, who is the man most likely to see a case of syphilis at its onset that an immediate diagnosis and institution of treatment before a positive blood Wassermann can be obtained is the only certain method of preventing the late manifestations of syphilis, particularly neurosyphilis. To wait for a positive blood Wassermann before starting treatment is in most cases criminal and it might almost be said that it is better to treat two cases of suspected primary syphilis which are not syphilis, than to allow one case to develop neurosyphilis. The best and most modern aids to diagnosis, particularly the dark field investigation of the secretions from the lesion and the most expert clinical opinion should be available and should be used before a penile sore is decided to be nonsyphilitic.

To wait till the signs of generalization occur is to invite neurosyphilis, for with the onset of the stage of generalization the *Spirochaeta pallida* swarm in the general circulation and are carried by it to every part of the body. It is probable that the blood vessels

of the central nervous system are filled with the organisms. In a large percentage of cases most of the *Spirocheta pallida* that are lodged there die off in the same manner as those lodged in every part of a diffuse rash apparently die off without treatment in the great majority of the lesions, for there is seldom a recurrence of every lesion of the early diffuse rash. The reasons why in a certain number of cases the *Spirocheta pallida* continue to live and multiply in the blood vessels of the brain and soon penetrate the tissues are unknown. It may be due to a special strain of the organism with affinity for nervous tissues, it may be due to the lowering of the resistance of the tissues of the central nervous system or it may be due to some other factor. Suffice it to say that conditions that tend to lower neuroresistance are probably helpful factors to the syphilitic invasion of the tissues. It is very probable that men with generalized syphilis who had been subjected to the terrific strain of trench life in France would be more prone to cerebrospinal syphilis than those who had not. Even every day conditions of twentieth century life are not conducive to the attainment of a strong neuroresistance against the invasion of this organism. The *Spirocheta pallida* that invade the nervous system do so in the very early stages of generalization and set up an inflammatory reaction of the tissues which can be determined in most cases, by examination of the cerebrospinal fluid. If the cerebrospinal fluid is negative during the stage of generalization to those inflammatory reactions which are considered to denote the presence of the *Spirocheta pallida*, in the large majority of cases, neurosyphilis will never develop if the patient is placed on systemic treatment and such treatment continued over a sufficient length of time. If treatment is allowed to lapse the organism may again invade the blood stream and be carried to the nervous system, there to set up a cerebrospinal syphilis, but if proper treatment is persisted in this will not occur. If the cerebrospinal fluid shows evidence of syphilitic invasion of the central nervous system during the stage of early generalization a long period may elapse before symptoms appear but in every case the patient has a definite neurosyphilis and clinical evidence of the disease will appear later. When this occurs treatment is more difficult and more dangerous to the individual and his finances than if treatment is instituted at the proper time, viz., in the presymptomatic stage.

Every case of generalized syphilis, whether early or late, and consequently every case that shows a positive Wassermann in the blood, and every case of late or asymptomatic syphilis should have at least one examination of the cerebrospinal fluid during the early part of his treatment. There are no signs produced by the syphilis that would indicate a possible invasion of the cerebrospinal system. Though the skin and nervous system are analogous structures embryologically, both being developed from the ectoderm, we have not found that marked skin lesions are indicative of central nervous involvement. In our series of cases of generalized, late and asymptomatic syphilis in which the cerebrospinal fluid has been examined we have found, that in those cases in which the cerebrospinal fluid did not indicate the presence of the *Spironema pallida*, 86 cases had marked involvement of the skin, varying from a macular rash to a diffuse nodular and gummatous condition, while sixty-six cases did not show any skin lesions. In those cases which we considered to be early neurosyphilis, thirty-one showed a negative skin and only twenty-nine showed skin involvement. None of these cases was as severe as the severe cases of the negative type. In the negative series out of 144 cases, six could give no history of syphilis, nor was there found on examination any indication of the usual syphilitic lesions. On the other hand out of 66 cases in the positive series, ten gave no history and no indications. One might almost infer that if a prognosis from the virulence of the syphilitic infection had to be made as to whether a case would develop neurosyphilis or not, those cases which showed very mild or practically negative signs of syphilis would be more prone to neurosyphilis than those in which the syphilis was malignant.

The condition of the blood Wassermann is no indication of cerebrospinal syphilis, particularly if the patient has received previous systemic treatment. This is especially true in cases of asymptomatic syphilis and on reference to the table it will be seen that a number of cases in the positive series have negative blood Wassermans but are positive in their cerebrospinal fluids.

It has been stated that neurosyphilis does not develop until about two years after the initial infection. In at least eight cases in our series the development of the neurosyphilis was considerably less than one year. Two cases are worthy of citation in this connection.

CASE 1.—Cadet R. Age 29. Generalized syphilis. Patient had a markedly indurated sear on penis, a diffuse maculopapular rash over trunk and extremities and mucous patches on the tonsils. Blood Wassermann strongly positive. His sore had appeared three months previous to his admission to hospital. He received 2 injections of neosalvarsan, which was all the treatment he had had previous to his lumbar puncture. Serologic findings: Cells 32, globulin +, Wassermann 0.0.0.2, Colloidal gold 0001100000.

CASE 2.—Private D. Age 32. Admitted to hospital with generalized syphilis and received seven injections of neosalvarsan and eight intramuscular injections of mercury. He gave no history of any previous sore and his sore had been present only eighteen days on admission. At the completion of the course his blood Wassermann was negative. About four months after his primary sore appeared and about six weeks after he completed his course of treatment he was seized by an attack of epileptiform convulsions, amounting almost to status. His cerebrospinal fluid finding about a week after the attack was: Cells 17, globulin ++, Wassermann 0.0.0.4.

Although cerebrospinal syphilis may even commence with clinical symptoms less than 6 months after the primary sore appears and may be present serologically in as short a period as three months without clinical symptoms, it is undoubtedly true that the older the syphilis the more likelihood there is of evidence of the *Spirochaeta pallida* in the cerebrospinal fluid. In those cases which gave completely negative serology the average duration of the syphilis was 14.1 weeks. In those cases that gave definitely positive serology the average duration of the syphilis was seven and one-fourth years.

To be satisfied with a neurologic examination of a syphilitic as proof whether cerebrospinal syphilis exists or not, is almost criminal. In the detailed report below it will be seen that many cases that were serologically neurosyphilis had no clinical neurologic manifestations. On entering the cerebrospinal system the *Spirochaeta pallida* set up an inflammatory reaction which is evident in the examination of the cerebrospinal fluid. When sufficient gross destruction has been produced to alter permanently nervous pathways then only do clinical neurologic signs appear. From the neurologist's point of view it is interesting and instructive to be able to make a diagnosis of the localization of the lesions, but from the patient's point of view to wait until such a definite diagnosis can be made from clinical findings is most disastrous, for the destroyed neurones can not be regenerated by any form of treatment. A little later we desire to lay stress on the importance of a clinical neuro-

logic examination as governing certain indications for treatment but from a diagnostic point of view with the welfare of the patient as a primary consideration the diagnosis of neurosyphilis should be made before clinical findings are manifested. In these early cases no more elaborate diagnosis is required.

There is only one certain method of diagnosing neurosyphilis when the diagnosis will be of great benefit to the patient and that is by examining the cerebrospinal fluid of every case of generalized, late and asymptomatic syphilis.

In this connection it will be well to point out the necessity of a lumbar puncture and an examination of the cerebrospinal fluid and blood in every case of nervous disease, particularly in obscure conditions. We could enumerate a great number of cases which have passed through our hands at this hospital with neurosyphilis which had been treated previously elsewhere for other nervous conditions. It will be sufficient to cite two typical cases:

CASE 1.—Pte. M. Age 38. No history of syphilis obtainable nor were there any indications of a previous syphilitic skin condition. Two years ago this patient was admitted to a hospital where a diagnosis was made of musculospiral paralysis. No effort was made apparently to ascertain the cause, the paralysis improved and he was discharged as cured. He was admitted to this hospital with clinical tabes. Blood Wassermann moderately positive. Cerebrospinal fluid: Cells 120, globulin ++, Wassermann 4.4.4.4., Colloidal gold 0012321100.

CASE 2.—Major C. Age 42. Contracted syphilis eight years ago, for which he had very slight local treatment. One year later was treated by the Weir Mitchell method for neurasthenia. On admission to this hospital he showed signs of early paresis. Blood Wassermann strongly positive. Cerebrospinal fluid:—Cells 142, globulin ++, Wassermann 4.4.4.4., Colloidal gold 2233210000.

We consider it to be a self-evident fact that a physician who treats a case of generalized, late or asymptomatic syphilis, or of any nervous condition, without examining the cerebrospinal fluid is guilty of gross injustice toward his patient.

Lumbar puncture is a procedure with which every physician should be familiar. If done with proper care and good technic it is devoid of harmful results. The discomfort to the patient during the puncture itself is not greater than the discomfort experienced in having blood taken for a Wassermann. There is no reason why a lumbar puncture can not be done in the office and the patient sent home in a taxicab. In the large majority of cases one day is all the time that the patient need lose and in no case should it prevent

him from working for more than a week. As fine a needle as possible should be used, preferably gauge 22.* It is unnecessary to employ any anesthetic, either general or local. To use general anesthesia is as unnecessary as it would be to use it for an ordinary hypodermic injection. Local anesthesia would, in any case, only be necessary in a very nervous or excitable patient and in that type of case the introduction of the anesthetic would be more painful than the actual lumbar puncture. The technic we advise is as follows: With the patient in the erect posture a line connecting the crests of the ilia is painted across the back with tr. iodine. He then lies on his right side on a hard table. The right arm is kept close to his body while the left is passed around the neck of an assistant whom he is facing. The assistant draws up the patient's knees and bends the back so that the knees are as close to the chin as possible. The needle is inserted in the middle line into the interspace either just above the iodine line or two interspaces above. Care should be taken to introduce the point of the needle only just through the membranes. This is determinable easily in most cases as the needle can be felt to pass through the dura. Two tubes should be used to collect the fluid as the first may be slightly blood stained. Into the first tube about two-thirds of the amount to be withdrawn is taken, into the second the other third. Altogether not more than 3 c.c. of fluid should be withdrawn for the ordinary diagnostic test. This is all that is necessary for the performance of the four reactions and does not alter materially the intracranial pressure and consequently the patient should experience no immediate reaction. After the puncture is done the patient should be sent home and told to go to bed without a pillow and with the foot of the bed raised. He should remain in bed the next day and if no reaction occurs may be up and about the following morning.

In our series of 142 consecutive lumbar punctures 115 gave absolutely no reaction whatever. Twenty-two gave a slight reaction, consisting of headache, either frontal or occipital, commencing twenty-four hours after the lumbar puncture, present in the erect position but absent on lying down and lasting from two to three days. There was a more severe reaction in five cases. They suffered from severe frontal and occipital headache, a feeling of pressure on

*The gauge of needles mentioned in this article are those of Parke, Davis & Co., glassseptic hypodermic needles, to the caliber of which the needles we recommend conform.

the back of the neck, dizziness and faintness on standing up, vomiting and sleeplessness. These symptoms were practically absent when the patient was recumbent. They commenced about twenty-four hours after the lumbar puncture and lasted about a week. There did not seem to be more reactions present in those cases that gave a negative spinal fluid than in those in which the fluid was positive. If any difference between the two occurred there were proportionately slightly more reactions among the positives than the negatives. It is almost impossible to determine whether a patient will have a reaction after a lumbar puncture or not. Neurotic, high-strung individuals who fear pain or discomfort at the time of puncture or permanent injury as a result seem more susceptible than those who are not of the same type. This psychic element is undoubtedly the cause of reaction in a small percentage of cases but in the majority the reaction can be explained only on the basis of MacRobert's¹ theory. He states that the amount withdrawn viz., less than 3 c.c., is not sufficient to cause an alteration of intracranial pressure. The dura is a hard, resistant membrane and the needle hole remains patent. The withdrawal of the needle draws the pia through this hole so forming a little funnel by which the cerebrospinal fluid is drained off slowly into the extradural spaces. This gradual withdrawal of fluid lessens the bulk of the water bed on which the brain rests and on assuming the erect posture the base of the brain presses on the uneven surface of the skull with resultant symptoms. The hole in the dura takes four or five days to heal and the patient suffers until the normal amount of cerebrospinal fluid has been secreted again. We have tried many methods to prevent reaction, such as rotating the needle before withdrawing, withdrawing the needle rapidly, withdrawing it slowly, but we have not found any method that will absolutely prevent this reaction in a very small percentage of cases. For the treatment of the reaction the patient should be kept in bed until the puncture hole in the dura has healed and the headache and other symptoms have ceased. Drug treatment is unavailing.

Before detailing the significance of lumbar puncture findings and their indications for treatment it might be well to state the various methods at present in vogue for the treatment of neurosyphilis. In considering the question of diagnosis the statement was made that a neurologic examination was of no value from the standpoint of

the early recognition of cerebrospinal involvement but in late cases of syphilis a neurologic examination may reveal neurosyphilis, even though the cerebrospinal fluid is negative. After the irritative stage has passed and the *Spironema pallida* have penetrated the nervous tissue, the inflammatory reaction called forth during the stage of irritation may disappear. It is only when the coverings of the central nervous system are invaded that we get a positive cerebrospinal fluid. Every case of neurosyphilis primarily is an involvement of the meninges but the *Spironema pallida* may die out eventually in this situation while at the same time they are producing degenerative changes in the parenchyma. There is a question whether in these late degenerative cases the *Spironema pallida* themselves are present or whether it is merely a secondary degeneration due to the former presence of the organisms. Whatever is the cause it is undoubtedly true that a few cases of late neurosyphilis show a negative spinal fluid. One case might be cited to illustrate this:

Sergeant L. Age 26. Late syphilis. Admitted with gumma of the serotum. The syphilis was of two years' standing and he had had no treatment. The neurologic examination revealed a diminished right knee jerk, a moderate Romberg, poor sense of skin traction, inequality of the pupils and contracted field of vision. Blood Wassermann negative. The cerebrospinal fluid: Cells 1, globulin negative, Wassermann negative. Clinical diagnosis—tabes.

This type of case and also the fact that neurologic findings when present are important indications for the kind of treatment to be instituted show that before treatment is commenced a careful neurologic examination is necessary.

For the general treatment of neurosyphilis there are three methods in use that are directed to the destruction of the *Spironema pallida*. First, treatment by intravenous injections of salvarsan alone. Second, treatment by intravenous injections of salvarsan combined with the withdrawal of large amounts of cerebrospinal fluid at stated intervals. Third, the introduction of salvarsan in sera directly into the cerebrospinal fluid. Each one of these methods of treatment is useful and the indications for them will be considered under the discussion of the significance of each type of finding in the cerebrospinal fluid to be cited below. It is not necessary to detail any technic for the first two methods. There are various methods of technic for intraspinal injections of salvarsanized sera,

all of which are modifications of the original Swift-Ellis method. We have found the most advantageous to use to be that of Ogilvie.

Ogilvie's Method for the Preparation of Salvarsanized Serum.—The blood is centrifuged for a sufficiently long period of time to remove every red blood cell from the serum. Ten c.c. of this serum are taken and to it is added the dose of salvarsan which is to be given. The salvarsanized serum is then incubated at 37° C. for one hour and inactivated at 56° C. for one-half hour. The serum is then ready for administration. The shorter the time between the removal of the salvarsanized serum from the water-bath and its injection the better. In no case should it be used if it is more than one hour old. For fuller details concerning the preparation of the salvarsanized serum Ogilvie's² original paper should be consulted.

In administering salvarsanized sera the same technic should be followed as in doing an ordinary lumbar puncture, except that a larger needle should be used, preferably gauge 23A. Between 15 and 20 c.c. of fluid should be withdrawn. Then to the needle is attached a short piece of rubber tubing which is connected with a glass funnel. Sufficient fluid is allowed to flow through the tube until about 3 or 4 c.c. have collected in the funnel. The tubing is then cleared of air, the salvarsanized serum is poured into the funnel and the mixture of serum and cerebrospinal fluid is allowed to flow into the canal by gravity. When the serum is about to disappear into the tubing a little saline is added to wash through the tubing and the needle is withdrawn. Scrupulous sterility is, of course, necessary throughout. There is no reason why this treatment can not be given safely in office practice, the patient being placed in a taxi afterwards and sent home to bed, where he should remain without a pillow and with the foot of the bed elevated for thirty-six hours. In about half the cases treatment is followed by some reaction. There is usually headache and root pains in the legs and arms. These pains at times, may be severe, particularly in tabetic cases, but are usually easily controlled by aspirin. It is not often necessary to use opiates, for those cases which complain most bitterly are those cases in which opiates are inadvisable. Tabetics are prone to the loss of mental self-control and as a consequence opiates once commenced will have to be continued and by pandering to the patient's moral weakness hinder the effect of reeducational therapy. The reaction at times takes the form of precipitat-

ing symptoms but these usually pass off in a few days. It is but rarely necessary that the patient should be kept in bed forty-eight hours after treatment. He should, however, be visited on the evening of the day of treatment and the next day in order to relieve any reaction he might have.

When a large number of cases are to be treated at one time sufficient blood may be taken from one person to provide sera for all treatments. Approximately 40 c.c. of blood are required to provide sufficient serum for one treatment. If only one or two cases are to be treated it is better to use autogenous serum and in many cases when autogenous sera are being used a combination of Ogilvie's modification with the Swift-Ellis technic may be of value. The initial dose of salvarsanized serum is preferably 0.2 mg. of salvarsan in 10 c.c. of serum. Neosalvarsan should not be used. For the ordinary case of neurosyphilis a course of ten injections is sufficient for one period of treatment and this should be followed by at least six months without intraspinal treatment. The interval between treatments should be about ten days in those cases with none or slight neurologic signs. In cases with marked neurologic signs, particularly in tabes, the interval should be fourteen days. Should the first injection be followed by a severe reaction the interval should be lengthened, in the first case to fourteen days and in the second to three weeks. We would advise that in the ordinary case the first three injections should be 0.2 mg., the next three 0.3 mg., the next three 0.4 mg. and the tenth 0.5 mg. In using the combination of the Ogilvie and Swift-Ellis methods not more than 0.3 mg. of salvarsan should be added to the autosalvarsanized serum. More details concerning dosage, rest interval and precautions to be taken for the various types will be given later. Intraspinal treatment should nearly always be combined with systemic treatment. If the patient has no neurologic signs and his cerebrospinal fluid is made persistently negative over a number of years it can be presumed that his neurosyphilis is permanently arrested, if not completely eradicated. Should, however, the patient show clinical signs of a degenerative process having taken place in any part of the nervous system, the best that can be expected even from this form of therapy is that the cerebrospinal fluid may be made persistently negative and the signs prevented from increasing. Intraspinal treatment is directed towards the eradication of the Spi-

ronema pallida and can not be expected to replace destroyed neurones. Consequently in cases showing definite neurologic signs re-educational therapy for the purpose of making new pathways through the brain and cord should be combined with intraspinal treatment. In a certain percentage of tabetics and in a large percentage of paretics with marked evidence of degeneration intraspinal treatment itself is unavailing, but in the class of cases with which we are dealing and which is the type of case that should be treated for neurosyphilis before gross neurologic damage is done, we consider intraspinal therapy as an invaluable adjunct to treatment.

Intraspinal injections are not only of use in the treatment of neurosyphilis but are also an aid to diagnosis. The introduction of a small dose of salvarsanized serum into the spinal canal sets up a reaction analogous to the Herxheimer reaction in that, if syphilitic infection is present, the liberated toxins from the destroyed *Spirochaeta pallida* increase the inflammatory reaction and so cause the positivity of the fluid to increase. By this reaction, if a case is suspected from clinical indications to be neurosyphilis but is serologically negative, an injection of a small dose of salvarsanized serum may render the fluid positive. Two cases are illustrative of this:

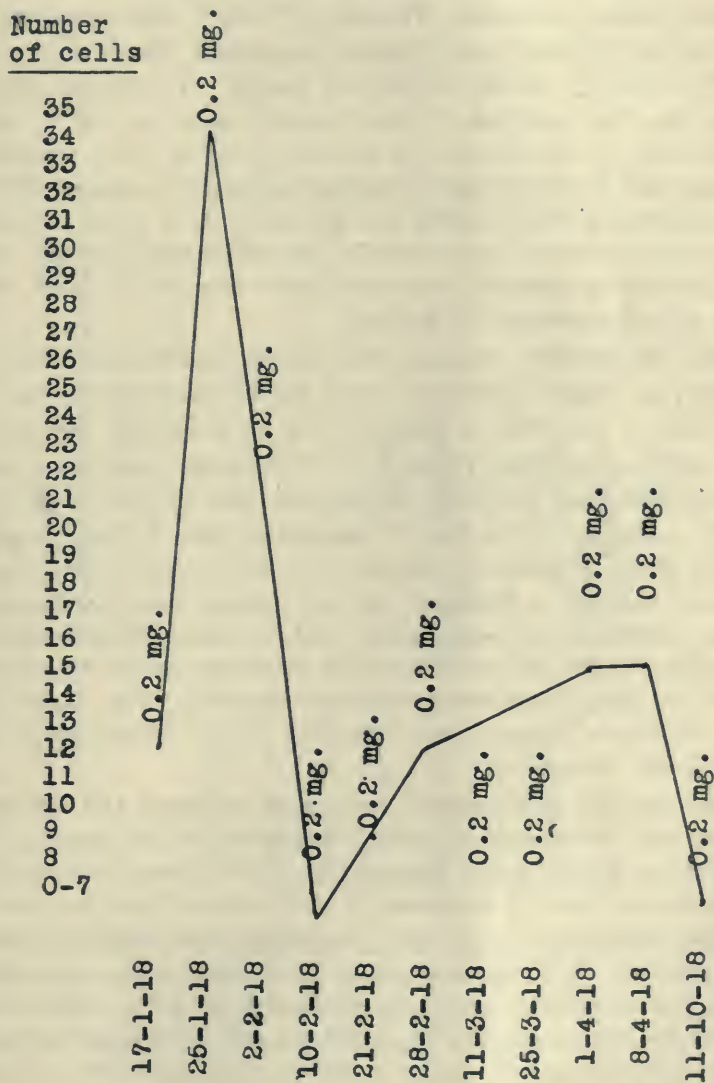
CASE 1.—Pte W. Age 45. Asymptomatic syphilis. Patient gave no history of syphilis, but complained of headache, loss of memory, poor attention and loss of business ability. Blood Wassermann strongly positive. Cerebrospinal fluid: Cells 2, globulin negative, Wassermann negative. He was given 0.2 mg. salvarsanized serum intraspinally. Eleven days later cerebrospinal fluid: Cells 14, globulin negative, Wassermann 0.0.0.4.

CASE 2.—Pte D. Age 38. Asymptomatic syphilis. Patient had clinical signs of tabes. Blood Wassermann strongly positive. Cerebrospinal fluid: Cells 6, globulin negative, Wassermann negative. He received 0.2 mg. salvarsanized serum intraspinally. Seven days later cerebrospinal fluid:—Cells 280, globulin ++, Wassermann negative. Colloidal gold 0000001100.

Care must be taken in reading the result of this provocative injection. An increased cell count or a positive colloidal gold are indications of the presence of neurosyphilis. A positive Wassermann, or an increased globulin alone are not, as these substances may have been introduced with the serum. The dose that should be used for provocative injections is 0.2 mg. and the examination of the cerebrospinal fluid should take place seven to fourteen days later.

Each one of the reactions in the cerebrospinal fluid alters differently as a result of treatment. The cell count, after the first injection, usually increases or remains stationary. Successive treat-

TABLE I.
REDUCTION OF CELL COUNT UNDER INTRASPINAL TREATMENT



ments produce a gradual diminution. At intervals throughout the course of treatment the cell count increases again, but each increase is less than the highest previous count. If the increased cell count is a result of a recent invasion of the *Spirocheta pallida* it falls rapidly to normal but the longer the duration of the organism in the nervous system the more slowly does the cell count return to normal under treatment. The chart (Table I) illustrates typically the course of the cell count under intraspinal treatment.

The globulin reaction fluctuates greatly. It may be increased after the first injection, it may remain stationary, or it may be decreased. If the globulin is strongly positive when treatment is commenced it will probably remain positive throughout life. The fluctuations of the globulin are dependent to a certain extent on the foreign proteins introduced in the salvarsanized serum, so that an increase in globulin in a case under treatment is little indication as to the progress of the case.

The Wassermann reaction also shows fluctuations which may depend on reagin introduced with the salvarsanized serum. The decrease in positivity is gradual with an occasional exacerbation, but under appropriate treatment it will become negative provided, at the same time, the blood Wassermann also becomes negative. A slight positivity of the fluid Wassermann with a strong positivity of the blood Wassermann may be only an indication that reagin is passing through a damaged chorioid plexus but if sufficient systemic treatment is being given and the fluid Wassermann was strongly positive at first intraspinal treatment should be continued until the fluid Wassermann becomes negative. The chart (Table II) illustrates typically the reduction of the Wassermann under intraspinal treatment.

The colloidal gold reaction is the most stubborn and resistant to treatment. Its presence is always indicative of the presence of the *Spirocheta pallida* and a diagnosis as to the form which the neurosyphilis will take, if treatment is not instituted, can be made frequently from the curve of a positive finding before clinical symptoms are evident. In the present state of our knowledge we would advise that treatment should be continued until the colloidal gold curve has become negative. After the first two injections of salvarsanized serum a tabetic or a cerebrospinal syphilitic gold curve

may change its characteristics to that of a paretic and these cases should receive as intensive treatment as is given to paresis.

To sum up the only certain method of determining whether the cerebrospinal system has been invaded by the *Spirocheta pallida* is by an examination of the cerebrospinal fluid. Neurologic ex-

TABLE II.

REDUCTION OF THE WASSERMANN UNDER INTRASPINAL TREATMENT



aminations should be done on every case to guard against overlooking the very small number of cases of neuroinvolvement with negative fluid findings. Should the diagnosis still be in doubt a provocative intraspinal injection should be given and the fluid examined between one and two weeks later. If the fluid finding

TABLE III
 CLASS A. TYPICAL SEROLOGIC FINDING. CELLS 0 TO 7. GLOBULIN NOT INCREASED. WASSERMANN 0.0.0.0.
 COLLOIDAL GOLD NEGATIVE.

CASE NO.	AGE	STAGE OF SYPHILIS	DURATION OF SYPHILIS	PREVIOUS TREATMENT	BLOOD WASS'N	CELLS	GLOBULIN	SERUM WASS'N	COLLOIDAL GOLD
1	26	Generalized	32 days	None	++	0	Negative	0.0.0.0	Not done
2	20	Generalized	3 years	Yes	Neg.	5	Negative	0.0.0	Not done
3	36	Generalized	2 months	None	++	2	Negative	0.0.0	Not done
4	34	Generalized	2 years	Yes	++	3	Negative	0.0.0	0000000000
5	25	Generalized	6 months	None	++	0	Negative	0.0.0	0000000000
6	28	Generalized	No history	None	++	5	Negative	0.0.0	Not done
7	27	Generalized	2 months	None	++	4	Negative	0.0.0	Not done
8	41	Generalized	1 year	Yes	++	0	Negative	0.0.0	Not done
9	20	Generalized	51 days	None	Neg.	4	Negative	0.0.0	Not done
10	25	Generalized	3 days	None	++	0	Negative	0.0.0	Not done
11	28	Generalized	28 days	None	++	3	Negative	0.0.0	Not done
12	21	Generalized	21 days	None	++	0	Negative	0.0.0	Not done
13	34	Generalized	42 days	None	Neg.	1	Negative	0.0.0	Not done
14	22	Generalized	30 days	None	Neg.	3	Negative	0.0.0	Not done
15	23	Generalized	15 days	None	++	3	Negative	0.0.0	Not done
16	22	Generalized	No history	None	++	2	Negative	0.0.0	Not done
17	37	Generalized	6 weeks	None	++	6	Negative	0.0.0	Not done
18	33	Generalized	Unknown	None	++	3	Negative	0.0.0	Not done
19	21	Generalized	8 months	Yes	++	2	Negative	0.0.0	Not done
20	30	Generalized	44 days	None	++	2	Negative	0.0.0	Not done
21	31	Generalized	11 days	None	Neg.	1	Negative	0.0.0	Not done
22	38	Generalized	15 months	None	++	5	Negative	0.0.0	Not done
23	20	Generalized	14 days	None	++	3	Negative	0.0.0	Not done
24	22	Generalized	14 days	None	Neg.	3	Negative	0.0.0	Not done
25	35	Generalized	7 years	Yes	++	5	Negative	0.0.0	Not done
26	23	Generalized	7 days	None	++	1	Negative	0.0.0	Not done
27	22	Generalized	7 days	None	Neg.	1	Negative	0.0.0	Not done
28	19	Generalized	20 months	Yes	++	2	Negative	0.0.0	Not done
29	32	Generalized	1 week	None	++	1	Negative	0.0.0	0000000000
30	23	Generalized	2 weeks	None	++	1	Negative	0.0.0	Not done
31	25	Generalized	6 months	Yes	Neg.	3	Negative	0.0.0	Not done
32	39	Generalized	35 days	None	++	3	Negative	0.0.0	Not done
33	28	Generalized	5 months	Yes	++	4	Negative	0.0.0	Not done

TABLE III (Cont'd.)

CASE NO.	AGE	STAGE OF SYPHILIS	DURATION OF SYPHILIS	PREVIOUS TREATMENT	BLOOD WASS'N	CELLS	GLORULIN	SERUM WASS'N	COLLOIDAL GOLD
34	20	Generalized	1 month	None	+++	1	Negative	0.0.0.0	Not done
35	22	Generalized	5 weeks	None	+++	1	Negative	0.0.0.0	Not done
36	25	Generalized	3 weeks	None	+++	2	Negative	0.0.0.0	Not done
37	33	Generalized	46 days	None	+++	7	Negative	0.0.0.0	Not done
38	21	Generalized	44 days	None	Neg.	1	Negative	0.0.0.0	Not done
39	29	Generalized	2 years	Yes	+	3	Negative	0.0.0.0	0000000000
40	21	Generalized	3 years	Yes	Neg.	5	Negative	0.0.0.0	Not done
41	23	Generalized	34 days	None	++	5	Negative	0.0.0.0	Not done
42	22	Generalized	14 days	None	Neg.	0	Negative	0.0.0.0	Not done
43	30	Generalized	58 days	None	+++	3	Negative	0.0.0.0	Not done
44	24	Generalized	14 days	None	+++	3	Negative	0.0.0.0	Not done
45	29	Generalized	2 months	None	+++	3	Negative	0.0.0.0	Not done
46	27	Generalized	46 days	None	+++	1	Negative	0.0.0.0	Not done
47	22	Generalized	5 weeks	None	Neg.	2	Negative	0.0.0.0	Not done
48	23	Generalized	8 years	Yes	+++	2	Negative	0.0.0.0	Not done
49	27	Generalized	6 months	Yes	+++	3	Negative	0.0.0.0	Not done
50	34	Generalized	Unknown	Yes	+++	4	Negative	0.0.0.0	Not done
51	24	Generalized	2 months	None	+++	6	Negative	0.0.0.0	Not done
52	28	Generalized	2 weeks	None	+++	2	Negative	0.0.0.0	Not done
53	25	Generalized	12 days	None	+++	2	Negative	0.0.0.0	Not done
54	36	Generalized	3 years	Yes	+++	2	Negative	0.0.0.0	Not done
55	34	Generalized	1 week	None	++	6	Negative	0.0.0.0	Not done
56	23	Generalized	Unknown	None	+++	2	Negative	0.0.0.0	Not done
57	20	Generalized	6 weeks	None	+	1	Negative	0.0.0.0	Not done
58	21	Generalized	53 days	None	++	2	Negative	0.0.0.0	Not done
59	28	Generalized	5 weeks	None	+++	2	Negative	0.0.0.0	Not done
60	34	Generalized	3 weeks	None	+++	2	Negative	0.0.0.0	Not done
61	29	Generalized	3 weeks	None	+++	2	Negative	0.0.0.0	Not done
62	19	Generalized	Unknown	Yes	+++	2	Negative	0.0.0.0	Not done
63	40	Generalized	6 years	None	+++	2	Negative	0.0.0.0	Not done
64	24	Generalized	1 year	Yes	+++	4	Negative	0.0.0.0	Not done
65	24	Generalized	5 months	None	+++	3	Negative	0.0.0.0	Not done
66	25	Generalized	16 days	None	Neg.	2	Negative	0.0.0.0	Not done
67	22	Generalized	40 days	None	Neg.	3	Negative	0.0.0.0	Not done
68	22	Generalized	3 months	None	+	2	Negative	0.0.0.0	Not done

TABLE III. (Cont'd.)

CASE NO.	AGE	STAGE OF SYPHILIS	DURATION OF SYPHILIS	PREVIOUS TREATMENT	BLOOD WASS'N	CELLS	GLOBULIN	SERUM WASS'N	COLLOIDAL GOLD
69	35	Late	1 year	None	++	6	Negative	0.0.0.0	Not done
70	25	Late	14 months	None	++	4	Negative	0.0.0.0	Not done
71	28	Late	6 years	None	++	0	Negative	0.0.0.0	0000000000
72	35	Late	14 years	Yes	++	2	Negative	0.0.0.0	0000000000
73	45	Late	No history	Yes	Neg.	2	Negative	0.0.0.0	Not done
74	44	Late	20 years	None	++		Negative	0.0.0.0	Not done
75	30	Late	2 years	Yes	+	2	Negative	0.0.0.0	Not done
76	28	Late	7 years	Yes	++	1	Negative	0.0.0.0	Not done
77	29	Late	8 years	Yes	++	3	Negative	0.0.0.0	Not done
78	25	Asymptomatic	2 years	None	++	3	Negative	0.0.0.0	Not done
79	25	Asymptomatic	Unknown	None	Neg.	0	Negative	0.0.0.0	Not done
80	26	Asymptomatic	4 weeks	None	++	0	Negative	0.0.0.0	Not done
81	50	Asymptomatic	No history	None	++	3	Negative	0.0.0.0	Not done
82	42	Asymptomatic	12 years	Yes	++	3	Negative	0.0.0.0	Not done
83	50	Asymptomatic	31 months	None	+	5	Negative	0.0.0.0	Not done
84	29	Asymptomatic	17 months	Yes	++	0	Negative	0.0.0.0	Not done
85	40	Asymptomatic	1 year	Yes	++	6	Negative	0.0.0.0	Not done
86	40	Asymptomatic	Unknown	None	++	2	Negative	0.0.0.0	0000000000
87	30	Asymptomatic	9 years	Yes	+	3	Negative	0.0.0.0	0000000000
88	24	Asymptomatic	Unknown	Yes	Neg.	6	Negative	0.0.0.0	Not done
89	35	Asymptomatic	12 years	Yes	++	4	Negative	0.0.0.0	Not done
90	40	Asymptomatic	12 years	Yes	++	3	Negative	0.0.0.0	0000000000
91	29	Asymptomatic	2 years	Yes	+	0	Negative	0.0.0.0	Not done
92	31	Asymptomatic	10 years	Yes	++	3	Negative	0.0.0.0	Not done
93	27	Asymptomatic	2 years	Yes	++	4	Negative	0.0.0.0	Not done
94	35	Asymptomatic	14 years	Yes	+	2	Negative	0.0.0.0	Not done
95	22	Asymptomatic	2 years	Yes	++	2	Negative	0.0.0.0	Not done
96	26	Asymptomatic	Unknown	Yes	++	6	Negative	0.0.0.0	Not done
97	33	Asymptomatic	6 years	None	++	3	Negative	0.0.0.0	Not done
98	42	Asymptomatic	6 months	Yes	Neg.	2	Negative	0.0.0.0	Not done
99	27	Asymptomatic	4 years	Yes	++	1	Negative	0.0.0.0	Not done
100	28	Asymptomatic	2 months	None	++	2	Negative	0.0.0.0	Not done
101	36	Asymptomatic	3 years	Yes	Neg.	3	Negative	0.0.0.0	Not done
102	28	Asymptomatic	No history	None	++	4	Negative	0.0.0.0	Not done
103	25	Asymptomatic	8 years	None	++	3	Negative	0.0.0.0	Not done

reveals the fact that the *Spironema pallida* is present in the central nervous system intensive treatment is required. If the invasion is early, systemic treatment may be sufficient to destroy the organism; if the stage of the invasion is later, intraspinal treatment is necessary. If the reaction of the fluid is not that indicative of the presence of the *Spironema pallida* systemic treatment is all that is required, but such cases should be watched closely as we are not yet in a position to say absolutely that the organism has not obtained a foothold.

The general considerations on the question of neurosyphilis having been dealt with, it is now necessary to consider our findings in the cerebrospinal fluid of syphilitics and their indications for treatment. If the serology of a case does not denote the presence of the *Spironema pallida* special treatment with reference to the nervous system is not required, but if the findings are indicative of the presence of the organism special treatment is then of the utmost importance. In our series of 210 cases of generalized, late, and asymptomatic syphilis, on all of which a neurologic examination has been done, we have classified the cerebrospinal fluid findings into six classes: (For the complete serologic report the table should be consulted.)

Class A.—(Table III).—Typical serology. Cells not increased over seven, globulin not increased, Wassermann negative, colloidal gold negative. One hundred and three cases, in all of which neurologic findings were negative. These cases have not been invaded as yet by the *Spironema pallida* and if proper systemic treatment is carried out the onset of neurosyphilis is exceedingly improbable.

Class B.—(Table IV).—Typical serology. Cells not increased over seven, globulin increased, Wassermann negative, colloidal gold negative. Forty-one cases, in all of which neurologic findings were negative. We do not consider that the *Spironema pallida* are present in the nervous system in these cases for reasons that will be detailed later. The treatment should be systemic and the syphilis controlled as rapidly as possible. Frequent examinations of the cerebrospinal fluid should be made in order to guard against the serology changing to that indicative of invasion by the *Spironema pallida*.

Class C.—(Table V).—Typical serology. Cells increased over seven, globulin not increased, Wassermann negative, colloidal gold

negative. Twelve cases. This class of case represents an early stage in the spironemal invasion of the nervous system. Systemic treatment should be commenced but if it is not sufficient to make the spinal fluid negative intraspinal treatment will have to be instituted.

Class D.—(Table VI).—Typical serology. Cells increased over seven, globulin increased, Wassermann negative, colloidal gold negative. Twelve cases. These represent a later stage of the invasion. Certain cases do well under systemic treatment, but the majority should be placed on intraspinal treatment.

Class E.—(Table VII).—Typical serology. Cells normal or increased over seven, globulin normal or increased, Wassermann negative, colloidal gold positive. Eight cases. If there is no pleocytosis, and the colloidal gold curve is not of the typical cerebrospinal syphilitic, tabetic, or parietic varieties, intensive systemic treatment may be all that is required. If the cell count is increased or the colloidal gold curve is of the cerebrospinal syphilitic, tabetic, or parietic types intraspinal treatment should be commenced immediately.

Class F.—(Table VIII).—Typical serology. Cells normal or increased over seven, globulin normal or increased, Wassermann positive, colloidal gold negative or positive. Thirty-four cases. If there are no clinical neurologic findings and the Wassermann alone is positive, or the Wassermann positive and the globulin increased but the cell count and the colloidal gold are normal, we do not consider that the *Spironema pallida* are present and the case should be treated in the same manner as Class B. If neurologic findings are present with the fluid findings given above, or if the cell count is increased or the colloidal gold positive with or without clinical neurologic signs, intraspinal treatment is a necessity.

Fuller details concerning our findings in this series of cases, our subclassifications, the reasons that we attach certain significance to certain findings and the details of treatment for each will be given below.

Class A.—(Table III).—Significance of the serologic finding cells not increased over seven, globulin not increased, Wassermann negative, colloidal gold negative.

SUMMARY

There were 103 cases in this class. Forty-three cases had primary sores still present, of which 27 were single papuloerosives, 11 were multiple papuloerosives, 2 papuloulceratives and 3 extragenitals. In 43 cases there were no skin lesions. Fifteen cases had a macular rash, 25 had a maculopapular rash, 2 had a pustular rash, 10 a papular, 4 had gummata, 2 had rupia, 1 a nodular and 1 a squamous syphilide. In 67 cases the mucous membranes were negative, 34 had mucous patches and 4 had condylomata about the anus. One case had epididymoorchitis, 2 had syphilis of the bladder, 1 case had a syphilitic lesion of the eye, 2 cases had laryngitis and 1 had syphilitic jaundice. Twenty-two cases had bad neurologic family histories. There was insanity in the family in 4 cases, epilepsy in one case, nervousness in 4 cases, apoplexy in 3 cases and alcoholism in 10 cases. Two cases had had previous nervous diseases. Seventy cases did not use alcohol, 4 used it very slightly, 10 slightly, 15 moderately and 4 to excess. The average duration of the syphilis previous to the lumbar puncture was 14.1 weeks. Thirty-six cases had had treatment for their syphilis previous to admission to this hospital, of whom 13 had received salvarsan. Five cases gave no history of syphilis. Neurologic examinations were practically negative except in a few cases where the abnormality could be accounted for by other conditions than the syphilis. Only 11 cases had any reaction after lumbar puncture and no reaction was severe.

PATHOLOGY AND TREATMENT

In those cases which are generalized syphilis it is probable that the *Spironema pallida* are situated in the lumen of the vessels of the central nervous system but have not yet penetrated into the nervous tissue itself. Treatment should be aimed at the immediate destruction of the organism in the general circulation. Therefore systemic therapy should be instituted and continued over sufficient length of time, preferably three years. In the case of late or asymptomatic syphilis if there are any *Spironema pallida* in the blood vessels they are in a nonactive condition and systemic treatment is sufficient for their destruction. If the systemic syphilis is kept well controlled neurosyphilis will not occur.

Vascular neurosyphilis may occur with a negative cerebrospinal fluid but as the neuro condition is secondary to a systemic lesion, viz., that of the blood vessels, special treatment is not necessary. If the systemic syphilis is kept well in hand by a vigorous systemic treatment the vascular lesions will not progress sufficiently to produce clinical neurologic signs.

Class B.—(Typical IV).—Significance of the serologic finding: Cells not increased over seven, globulin increased, Wassermann negative, colloidal gold negative.

SUMMARY

In our series of 210 consecutive cases 41 were of this type. In 20 cases primary sores were present, 14 of which were single papulo-erosives, 5 multiple papuloerosives, and 1 was a papuloulcerative. Twenty-three cases showed no skin lesions, 15 showed an early macular eruption and 1 had a maculopapular rash. Twenty-five cases had normal mucous membranes, 17 had mucous patches and 1 had condylomata about the anus. There was 1 case of a syphilitic involvement of the eye and 1 case had laryngitis. In the family histories only 5 gave evidence indicating a possible hereditarily weakened nervous system. Only 2 cases gave a history of past diseases tending to a defective neuro resistance. Twenty-five cases did not use alcohol, 8 used it slightly, 7 moderately and 1 to excess. Eighteen cases had had previous treatment with salvarsan over a period extending from one to eight years. Three cases had had previous mercurial treatment only. The average length of the syphilis previous to the examination of the cerebrospinal fluid was two and one-half years. In 1 case no history of syphilis was obtainable. Neurologically these cases showed no clinical signs except in occasional instances where local conditions would largely account for the disordered reflexes. After lumbar puncture 6 cases showed a reaction. In 4 cases this reaction was slight. Two cases had a more severe reaction with persistent headache, vomiting and neuromuscular pains lasting nearly a week.

PATHOLOGY

In considering the significance of any finding of the cerebrospinal fluid the important point to determine is whether the organism itself

TABLE IV
CLASS B. TYPICAL SEROLOGIC FINDING. CELLS 0 TO 7. GLOBULIN INCREASED.
WASSERMANN 0.0.0. COLLOIDAL GOLD NEGATIVE.

CASE NO.	AGE	STAGE OF SYPHILIS	DURATION OF SYPHILIS	PREVIOUS TREATMENT	BLOOD WASS 'N	CELLS	GLOB-ULIN	SERUM WASS 'N	COLLOIDAL GOLD
1	21	Generalized	8 months	Yes	++	1	+	0.0.0	0000000000
2	34	Generalized	21 days	None	+	1	+	0.0.0	0000000000
3	25	Generalized	18 months	Yes	+	2	++	0.0.0	Not done
4	25	Generalized	3 weeks	None	+++	4	++	0.0.0	Not done
5	38	Generalized	28 days	None	+++	3	++	0.0.0	0000000000
6	33	Generalized	129 days	None	+++	3	+	0.0.0	Not done
7	38	Generalized	6 years	None	+++	6	+	0.0.0	Not done
8	43	Generalized	No history	None	++	1	+	0.0.0	Not done
9	24	Generalized	21 days	None	+++	2	+	0.0.0	Not done
10	22	Generalized	15 months	Yes	Neg.	1	+	0.0.0	Not done
11	35	Generalized	10 months	Yes	+++	1	+	0.0.0	0000000000
12	42	Generalized	8 months	Yes	Neg.	3	++	0.0.0	Not done
13	25	Generalized	1 year	Yes	+	6	+	0.0.0	Not done
14	18	Generalized	83 days	None	+++	4	++	0.0.0	Not done
15	24	Generalized	1 year	Yes	+++	6	+	0.0.0	Not done
16	48	Generalized	21 days	None	+++	4	+	0.0.0	Not done
17	36	Generalized	26 months	None	+++	3	+	0.0.0	Not done
18	24	Generalized	7 months	Yes	Neg.	2	+	0.0.0	Not done
19	30	Generalized	10 days	None	+++	1	+	0.0.0	Not done
20	20	Generalized	1 year	Yes	+++	2	+	0.0.0	Not done
21	23	Generalized	75 days	None	Neg.	4	+	0.0.0	Not done
22	20	Generalized	7 days	None	+++	3	++	0.0.0	Not done
23	50	Generalized	7 days	None	+++	4	+	0.0.0	Not done
24	24	Generalized	30 months	Yes	+++	2	+	0.0.0	Not done
25	25	Generalized	5 days †	None	Neg.	0	+	0.0.0	Not done
26	21	Generalized	74 days	Yes	Neg.	6	+	0.0.0	Not done
27	25	Generalized	4 days †	None	Neg.	6	++	0.0.0	0000000000
28	32	Generalized	6 days	None	+++	1	+	0.0.0	Not done
29	22	Generalized	9 days	None	+++	2	+	0.0.0	Not done
30	20	Generalized	26 days	None	+++	4	+	0.0.0	Not done
31	30	Generalized	5 months	None	Neg.	2	+	0.0.0	Not done
32	30	Generalized	3 months	None	++	2	+	0.0.0	Not done
33	30	Late	5 years	Yes	++	3	+	0.0.0	Not done
34	27	Asymptomatic	2 years	Yes	+++	0	+	0.0.0	0000000000
35	31	Asymptomatic	4 months	Yes	+++	0	+	0.0.0	Not done
36	23	Asymptomatic	2 years	Yes	+++	6	+	0.0.0	0000000000
37	18	Asymptomatic	8 months	None	+++	3	+	0.0.0	Not done
38	30	Asymptomatic	5 years	Yes	+	3	++	0.0.0	0000000000
39	40	Asymptomatic	12 years	Yes	+++	2	+	0.0.0	Not done
40	47	Asymptomatic	17 years	Yes	+++	2	+	0.0.0	Not done
41	42	Asymptomatic	2 years	Yes	++	6	++	0.0.0	0000000000

is present in the tissues or not. The factor that is concerned in the production of globulin in the cerebrospinal fluid has not been determined as yet. It may be manufactured by the meninges, it may pass through the filter of the chorioid plexus from the blood, or it may be produced by a combination of these factors. In the case of an infection of the meninges by an organism the amount of globulin is increased. This is particularly true in the case of syphilis. But in the case of syphilis if the organism itself is eradicated the increase in globulin may persist showing that permanent alteration has taken place in the structures concerned in its production. As the first sign of a spirochetal invasion of the meninges is an increased cell count it would be expected that if the increase of globulin were due to the presence of the organism in the meninges it would be accompanied by a pleocytosis. Also if the spirochetal damage to the meninges produced a permanent increase in the globulin the pleocytosis would also be permanent. This is not the case, however, for the cell count falls to normal while the globulin increase persists. It seems probable, therefore, that the factor that produces the excess of globulin is damage, not to the meninges, but to the filter of the chorioid plexus. This damage may be produced by either the actual presence of the organism or by the action of the syphilo-toxins. In late cases of neurosyphilis with marked clinical signs the persistence of the increase of globulin is a result of a previous presence of the *Spirocheta pallida* but in the class of cases that we are dealing with, where there are no clinical neurologic signs and where the infection is recent, late neurosyphilitic conditions are not to be expected. In early cases of neurosyphilis if the organism were present there would undoubtedly be a pleocytosis. As this does not occur the excess of globulin can not be attributed to the presence of the *Spirocheta pallida* in the tissues of the nervous system and in all probability it is due to the action on the filter of the chorioid plexus of the toxins circulating in the blood stream. We do not consider, therefore, that the increase in globulin alone in the cerebrospinal fluid of an early case of syphilis without neurologic signs is indicative of the actual presence of the *Spirocheta pallida*. We will detail some further reasons for this belief in discussing the significance of the Wassermann findings.

TREATMENT

We do not consider that the *Spironema pallida* itself is present in the central nervous system in these cases. The damage done to the filter of the chorioid plexus is caused by the toxins which are circulating in the blood and are produced by the general systemic infection. As a consequence it is not necessary that the cerebrospinal system should receive special local treatment aiming at the destruction of the organism. As soon as the general systemic infection is well under control the toxins are no longer circulating in large amounts and no further damage to the central nervous system need be expected. On the other hand the toxins produce a *locus minor resistentiæ*, and if the general systemic infection is not checked promptly and kept well controlled *Spironema pallida* circulating in the blood may lodge there and find an easy medium in which to multiply.

The treatment that we advise in this class of case is as follows: When the condition of the cerebrospinal fluid has been discovered the patient should be given intensive arsenical and mercurial treatment. A warning as to the dangers of too intensive treatment and to the necessity for treatment of the syphilized individual rather than of the syphilis alone need not here be appended. These facts should be familiar to every physician who attempts to treat any case of syphilis. At the end of three months a second lumbar puncture should be made and the cerebrospinal fluid examined. If the fluid is then negative, the general systemic treatment should be continued as long as it is thought necessary, the cerebrospinal fluid being examined twice a year. If the fluid continues to be negative we believe that the patient should have three to four years general treatment followed by one year without treatment. If a lumbar puncture be done at the end of this period and the serologic finding is negative, there is strong probability that the patient has been protected from cerebrospinal infection.

Should the second or later lumbar punctures show globulin to be present either in the same or increased amounts similar treatment should be followed. There is a possibility that the damage to the chorioid plexus may have been sufficiently great to allow the excess of globulin to pass permanently into the cerebrospinal fluid. To make certain, however, we would advise that the patient be given

a provocative intraspinal injection at some time before the final lumbar puncture is done. Should the fluid examination then show only the increased globulin, the reason for it is due to the permanent damage done to the filter.

Should the second lumbar puncture or any subsequent lumbar puncture show a pleocytosis a positive colloidal gold or a positive Wassermann, the case should then be dealt with as belonging to one of the other types and treated accordingly.

Class C.—(Table V).—The significance of the serologic finding, cells increased over 7, globulin not increased, Wassermann negative, colloidal gold negative.

SUMMARY

There were 12 cases belonging to this type, 10 of them were generalized syphilis and 2 were asymptomatic syphilis. In 5 cases primary sores were still present, 3 were of the papuloerosive type, 1 of the papuloerosive multiple type and 1 of the papulo-ulcerative type. In 2 cases the skin was negative. Two had a macular rash, 3 had a maculopapular rash, 3 a papular rash and 1 had gummata. Five cases had negative mucous membranes, 6 had mucous patches in the mouth and 1 had condylomata about the anus. One case had a bad neurologic family history and 2 cases had a history of previous nervous diseases. Three cases did not use alcohol, 1 used it very slightly, 1 slightly, 6 moderately and 1 to excess. Four cases had had previous treatment for their syphilis. The average length of syphilitic infection was 10.5 months varying from 46 days to 4½ years. Two cases gave no history of syphilis. Three cases complained of symptoms that might be attributable to an onsetting cerebrospinal syphilis such as frequency and urgency, headache and poor vision, though the latter was probably due to a local condition of the eye. Neurologically the large majority of the cases were normal. Two cases had a delayed bulbocavernosus reflex, 2 cases had a marked Romberg, 1 case had marked incoordination and 3 were slightly incoordinated. Following the lumbar puncture 2 cases complained of slight headache. The remaining 10 did not experience any ill effects.

TABLE V
CLASS C. TYPICAL. SEROLOGIC FINDING. CELLS INCREASED OVER 7. GLOBULIN NOT INCREASED.
WASSERMANN NEGATIVE. COLLOIDAL GOLD NEGATIVE.

CASE NO.	AGE	STAGE OF SYPHILIS	DURATION OF SYPHILIS	PREVIOUS TREATMENT	BLOOD WASSERMAN	CELLS	GLOBULIN	SERUM WASSERMAN	COLLOIDAL GOLD
1	25	Generalized	3 months	None	+++	22	Negative	0.0.0.0	Not done
2	21	Generalized	76 days	None	+++	13	Negative	0.0.0.0	Not done
4	37	Generalized	6 weeks	None	+	11	Negative	0.0.0.0	0000000000
3	27	Generalized	15 months	Yes	+++	15	Negative	0.0.0.0	0000000000
5	27	Generalized	2 months	None	+	22	Negative	0.0.0.0	Not done
6	23	Generalized	46 days	None	+++	10	Negative	0.0.0.0	Not done
7	21	Generalized	13 months	Yes	+++	14	Negative	0.0.0.0	Not done
8	41	Generalized	56 days	None	+++	8	Negative	0.0.0.0	Not done
9	34	Generalized	4½ years	Yes	+++	9	Negative	0.0.0.0	Not done
10	23	Generalized	No history	None	+++	9	Negative	0.0.0.0	Not done
11	33	Asymptomatic	9 months	Yes	+	8	Negative	0.0.0.0	Not done
12	45	Asymptomatic	No history	None	Neg.	18	Negative	0.0.0.0	Not done

PATHOLOGY

Probably the first reaction produced by the action of any irritant on the cerebrospinal meninges is an increase in the number of cells. The normal cell count may be considered to be between 1 and 7, between 7 and 14 may be called borderline and over 14 the cell count is definitely pathologic. The diagnostic significance of cell counts above 14 need not here be considered. Though this increased cell count may be produced by the admission of any irritant to the cerebrospinal canal it is improbable that the action of the syphilitic toxin alone can be sufficient to be the exciting factor, for in many cases that gave a negative cell count the systemic toxemia of the syphilis was more pronounced than in these cases with pleocytosis. It would seem, therefore, that the irritation which calls forth this reaction is dependent upon the presence of the *Spirocheta pallida* itself in the central nervous system. Though the organism is present in these cases it has not been so for a sufficiently long period or in large enough numbers to produce gross neurologic symptoms, either those of irritation or degeneration. In the cases with cell counts between 7 and 14 the invasion is probably just commencing. In the case of the cell counts over 14 the invasion has completely taken place but in neither type has the presence of the organism been extensive or prolonged enough to produce the tissue reaction of the Wassermann or colloidal gold. These would undoubtedly follow had the case not been examined, and treated until a further period of time had elapsed.

TREATMENT

As the *Spirocheta pallida* is undoubtedly present in these cases treatment will have to be directed with special attention to the nervous system. Should the cell count be borderline or moderately increased, it is not necessary to institute intraspinal therapy immediately. In fact in no case of this type, unless there are special indications neurologically, should intraspinal treatment with injections of salvarsanized serum be commenced until general systemic treatment has been tried for a short period of time and found to be unsuccessful. The *Spirocheta pallida* can usually be destroyed by the arsenic that passes from the blood to the cerebrospinal fluid and it is surprising how quickly a cell count will fall to

normal under general treatment alone. After the cerebrospinal fluid has been examined and the case found to belong to this type, the patient should be continued on intensive systemic and mercurial treatment. At the end of a short period, approximately 2 or 3 months, a second lumbar puncture should be done. If the cell count is then normal and the other findings still remain negative, systemic treatment should be continued in the same manner as detailed in the preceding class. The cerebrospinal fluid should be examined at half yearly intervals. If it remains normal throughout and is normal 2 years after systemic treatment has been completed, the *Spironema pallida* have probably been destroyed. Two cases are worthy of citation as illustrating this form of treatment in these cases:

CASE 1.—Pte. M. Age 25. Diagnosis:—Generalized syphilis, gummata and mucous patches being present. A neurologic examination revealed no signs of neurosyphilis. Blood Wassermann strongly positive. After patient had received two injections of salvarsan a lumbar puncture was done with the serologic finding of:—Cells 22, globulin negative, Wassermann negative. He received six more intravenous injections of salvarsan and two months after the first lumbar puncture a second was done. Serologic finding: Cells 2, globulin negative, Wassermann negative.

CASE 2.—Sergeant H. Age 27. Diagnosis:—Generalized syphilis. Patient had a papuloerosive sore and a maculopapular rash. There were no neurologic signs of neurosyphilis. Blood Wassermann slightly positive. After patient had received two injections of salvarsan a lumbar puncture was done with the fluid report: Cells twenty-two, globulin negative, Wassermann negative. He received five more intravenous injections of salvarsan and a month after the first lumbar puncture a second was done. Serologic finding:—Cells two, globulin negative, Wassermann negative.

It is very probable that if cases belonging to this type receive sufficient systemic antisyphilitic treatment the fluid will always remain negative and the cerebrospinal syphilis may be considered to be cured. During the whole course of treatment, however, at least half yearly examinations of the cerebrospinal fluid should be made in order that the possibility of this only being a temporary improvement can be carefully controlled.

Should the second lumbar puncture or subsequent lumbar punctures reveal an increased or stationary cell count intraspinal treatment should be instituted. In these cases treatment should be given once every ten days unless a severe reaction is provoked, in

which case the interval should be lengthened. We would advise that the patient be given at least 8 injections commencing with 0.2 mg. dose and gradually increasing until 0.5 mg. dosage is reached. At the same time systemic treatment should be continued. If the fluid is negative at the end of this course further half yearly examinations should be made over a period of 3 to 4 years, the last being made 3 years after all treatment has ceased. Should any of the examinations reveal an increased cell count a second course of intraspinal treatment should be commenced. If at the end of the first course the fluid still shows a pleocytosis, we would advise 2 more injections and if the fluid is then still positive a rest of 6 months and a repetition of the course of 10 injections.

Should at any time the fluid show positivity in the globulin, Wassermann or colloidal gold treatment should be carried out along the lines that are recommended for that type.

Class D.—(Table VI).—Significance of the serologic finding: Cells increased over 7, globulin increased, Wassermann negative, colloidal gold negative.

SUMMARY

There were 12 cases in our series that gave this finding. Ten cases were generalized syphilis, 1 was late and 1 was asymptomatic. Only 1 case had a primary sore present and this was of the papulo-erosive type. Six cases were negative for syphilitic skin lesions, 1 case had a macular rash, 4 had a maculopapular rash and 1 had secondary syphilides on the scrotum. Nine cases had negative mucous membranes, 3 had mucous patches and 1 had condylomata about the anus. One case had a syphilitic lesion of the eye and 1 case had periostitis of the tibia. Two cases had a familial history of alcoholism. All cases had a negative neurologic personal history. Six cases did not use alcohol, 1 used it very slightly, 1 slightly, 3 moderately and 1 to excess. Four cases had had previous treatment for their syphilis. The average length of the syphilitic infection was $5\frac{1}{2}$ months. One case gave no history of syphilis. Two cases gave a history of symptoms. One had frequency and urgency and the other suffered from headache. The large majority of these cases gave normal neurologic findings. In 1 case the knee jerks were sluggish, in 1 they were slightly increased. One case showed

TABLE VI
CLASS D. TYPICAL SEROLOGIC FINDING. CELLS INCREASED OVER 7. GLOBULIN INCREASED.
WASSERMANN NEGATIVE. COLLOIDAL GOLD NEGATIVE.

CASE NO.	AGE	STAGE OF SYPHILIS	DURATION OF SYPHILIS	PREVIOUS TREATMENT	BLOOD WASS'N	CELLS	GLOBULIN ULIN	SERUM WASS'N	COLLOIDAL GOLD
1	36	Generalized	7 days †	None	+++	43	++	0.0.0.0	Not done
2	25	Generalized	27 days	None	+++	10	+	0.0.0.0	Not done
3	26	Generalized	2 years	Yes	+++	23	+	0.0.0.0	Not done
4	28	Generalized	81 days	None	+++	23	+++	0.0.0.0	0000000000
5	22	Generalized	10 years	Yes	+++	20	+	0.0.0.0	Not done
6	24	Generalized	8 months	Yes	+++	13	+	0.0.0.0	Not done
7	22	Generalized	6 days †	None	Neg.	33	++	0.0.0.0	Not done
8	52	Generalized	3 weeks	None	+++	14	+	0.0.0.0	Not done
9	38	Generalized	6 weeks	None	+++	8	+	0.0.0.0	Not done
10	26	Generalized	4 days †	None	+++	9	+	0.0.0.0	Not done
11	22	Late	No history	None	+++	11	+	0.0.0.0	Not done
12	36	Asymptomatic	7 months	Yes	Neg.	8	++	0.0.0.0	0000000000

a moderate Romberg and 1 case was slightly incoordinated. The case that showed sluggish knee jerks had also inequality of the pupils and early mental symptoms. Only 1 case showed a reaction after lumbar puncture; this was severe with headache and vomiting lasting nearly a week.

PATHOLOGY

In a recent case of syphilis when the globulin is the only abnormal finding in the cerebrospinal fluid there is strong presumption that it is merely a filtrate from the blood due to damage to the filter of the chorioid plexus by the syphilotoxins in the general circulation. When a pleocytosis is the only abnormal finding in the fluid it seems fairly certain that the *Spironema pallida* are present in the central nervous system but the duration there has not been long nor the location widespread. When the serologic finding gives both a pleocytosis and an increased globulin the case is probably more advanced than that which gives only an increased cell count. The cell count in these cases is on the average a little higher than in the type in which the globulin is negative, showing that more time has elapsed to allow the tissues to produce their inflammatory reactions against the invader. As a consequence, these cases are more advanced than the preceding type but not yet sufficiently to have produced gross irritation or destruction of the nervous tissue itself and so usually have no clinical neurologic signs. If proper treatment is delayed in these cases the onset of signs of destruction of the tissue itself will be a matter of but a short time.

TREATMENT

Though no clinical diagnosis can be made with any great degree of reliability as to the exact type of neurosyphilis, with the early stage of which we are dealing, these cases are undoubtedly cases of cerebrospinal syphilis and the *Spironema pallida* are present definitely in the nervous system. Consequently the treatment of the syphilis must be combined with very careful and minute attention to the condition of the central nervous system. Each individual case must be carefully studied in order to determine whether combined systemic and intraspinal treatment should be instituted or whether the treatment should be only intravenous.

In most cases we believe it to be advisable to place the patient on intravenous treatment first. The intravenous treatment itself may be sufficient to vanquish the *Spironema pallida*. If such is not the case intraspinal treatment should be commenced. In the ordinary case with no definite neurologic signs, the patient should be placed on intensive arsenical and mercurial treatment. At the end of two or three months a second lumbar puncture should be done. If both the cell count and the globulin are normal the systemic treatment should be continued over a period of three to four years with half yearly examinations of the cerebrospinal fluid. Should the cerebrospinal fluid be negative throughout the period of treatment and remain negative two years after all treatment has ceased, the *Spironema pallida* may be considered to have been eradicated from the central nervous system. Two cases may be cited illustrating this method of treatment.

CASE 1.—Pte. H. Age 36. Generalized syphilis, a maculopapular rash being present. No clinical signs of neurosyphilis. Blood Wassermann strongly positive. Patient received two intravenous injections of salvarsan and a lumbar puncture was done. Serologic finding: Cells forty-three, globulin ++, Wassermann negative. He received two more injections of salvarsan and three weeks after the first lumbar puncture a second was done. Serologic finding: Cells seventeen, globulin +, Wassermann negative. He received four more intravenous injections of salvarsan and a month later a third lumbar puncture was done. Serologic finding: Cells six, globulin +, Wassermann negative.

CASE 2.—Pte. K. Age 28. Generalized syphilis, a rash and mucous patches being present. The duration of syphilis was eighty days. Neurologic examination showed sluggish knee jerks, slight inequality of the pupils and mild mental symptoms. Blood Wassermann strongly positive. He received three intravenous injections of salvarsan and a lumbar puncture was done. Serologic finding: Cells 23, globulin ++, Wassermann negative, colloidal gold negative. He received four more intravenous injections of salvarsan and two months after the first lumbar puncture a second was done. Serologic finding:—Cells eleven, globulin negative, Wassermann negative.

That these cases are more deeply invaded by the *Spironema pallida* is shown by the relatively slow reduction of the fluid finding by intravenous treatment compared with the cases cited in the previous type. None of these cases could be considered negative and they had to be discharged from hospital on account of the exigencies of the service, but we believe that if proper treatment were carried out this gradual reduction to normal of the pathologic findings would continue under systemic treatment.

Should the second lumbar puncture reveal a stationary or increased cell count and globulin it is advisable to commence combined intravenous and intraspinal treatment. The same holds good if the fluid has progressed towards normal under systemic treatment and then later become pathologic. The course should consist of ten injections, commencing with 0.2 mg. dosage and gradually increasing to 0.5 mg. dosage at ten day intervals. If the reactions are severe the interval should be lengthened to fourteen days. If the fluid is negative on the completion of this course, and remains negative, no further intraspinal treatment is necessary. If it should be positive at the end of the course two more injections, each of 0.5 mg. dosage should be given. If the fluid is then still positive the patient should receive six months rest from intraspinal treatment followed by a second course depending on the condition of the cerebrospinal fluid. If the fluid should become positive after being negative another course should be given. Combined intraspinal and intravenous treatment works well in these cases as may be illustrated by the following two cases:

CASE 1.—Pte. M. Age 58. Asymptomatic syphilis. Duration of infection eleven years. Neurologic findings negative, but patient had mental symptoms. Blood Wassermann negative. Cerebrospinal fluid:

20/5/18 Cells 120, globulin ++, Wassermann negative.
Placed on three months mercury and potassium iodide.
31/5/18 0.2 mg. Arsenolized serum intraspinally.
4/7/18 0.2 mg. Arsenolized serum intraspinally.
11/7/18 0.2 mg. Arsenolized serum intraspinally.
18/7/18 0.2 mg. Arsenolized serum intraspinally.
C.S.F. Cells 118, globulin ++, Wassermann negative.
1/8/18 0.2 mg. Arsenolized serum intraspinally.
8/8/18 0.2 mg. Arsenolized serum intraspinally.
15/8/18 0.2 mg. Arsenolized serum intraspinally.
C.S.F. Cells one, globulin negative, Wassermann negative.

Mental symptoms had almost entirely disappeared.

CASE 2.—Pte. N. Age 45. Asymptomatic syphilis. Duration of syphilis fifteen years. He had received in all two months' mercury. There were no neurologic signs. Blood Wassermann strongly positive. Cerebrospinal fluid:

19/4/18 Cells thirty-one, globulin +, Wassermann negative.
Was given eleven injections of salvarsan over a period of three months.
29/4/18 0.2 mg. Arsenolized serum intraspinally.
6/5/18 0.2 mg. Arsenolized serum intraspinally.
C.S.F. Cells 66, globulin +. Wassermann 0.0.0.4.

16/5/18	0.2 mg. Arsenolized serum intraspinally.
23/5/18	0.2 mg. Arsenolized serum intraspinally.
31/5/18	0.2 mg. Arsenolized serum intraspinally.
20/6/18	0.2 mg. Arsenolized serum intraspinally.
C.S.F. Cells 13, globulin +, Wassermann negative.	

The increase in cells and the slightly positive Wassermann one week after the first injection are produced by the provocative action of the first intraspinal treatment. We do not consider either of these cases cured. We believe both should be continued on mild systemic treatment with half yearly examinations of the cerebrospinal fluid for four or five years and a final examination two years after completion of all treatment. Should their fluid remain stationary or become negative no further intraspinal treatment is required. Should it become more pathologic another course or courses of intraspinal treatment should be given.

If at any time during the treatment of this class of case the type reaction of the fluid should change to that of another type, treatment should be adopted as for that type.

Class E.—(Table VII).—Significance of the serologic finding: Cells normal or increased, globulin increased, Wassermann negative, colloidal gold positive.

SUMMARY

There were 8 cases of this type, 7 were generalized and 1 was asymptomatic syphilis, 3 cases had primary sores still present, 1 had a single papuloerosive, and 2 had multiple papuloerosives. In 2 cases the skin was negative, 3 had a macular rash, 1 a papular, 1 a miliary, and 1 had rupia. Six had negative mucous membranes, 1 had mucous patches, and 1 had condylomata about the anus. One case had a synovitis of the knee joint with wasting of the muscles of the leg. Two cases had an alcoholic family history. One case had suffered from a psychoneurosis. Two cases did not use alcohol, 5 used it slightly, and 1 used it moderately. The average length of syphilis was 4 years. Three cases had had previous treatment with salvarsan. Five cases showed symptoms of an onsetting neurosyphilis. One had mental deterioration, 1 had frequency and urgency, 3 suffered from headaches, 1 from neuromuscular pains and 1 had a trophic disturbance. Neurologically 1 case showed night blindness, one case had weakness of the right facial nerve, 5 cases had

TABLE VII
CLASS E. TYPICAL SEROLOGIC FINDING. CELLS NORMAL OR INCREASED. GLOBULIN NORMAL OR INCREASED.
WASSERMANN NEGATIVE. COLLOIDAL GOLD POSITIVE.

CASE NO.	AGE	STAGE OF SYPHILIS	DURATION OF SYPHILIS	PREVIOUS TREATMENT	BLOOD WASS'N	CELLS	GLOBULIN	SERUM WASS'N	COLLOIDAL GOLD
1	30	Generalized	1 month	None	++	3	+	0.0.0.0	0012100000
2	21	Generalized	28 days	None	+++	1	+	0.0.0.0	0011000000
3	26	Generalized	2 years	Yes	Neg.	2	++	0.0.0.0	0001100000
4	33	Generalized	7 months	None	+++	2	++	0.0.0.0	0011100000
5	37	Generalized	64 days	None	+++	1	+	0.0.0.0	0001100000
6	33	Generalized	3 years	Yes	+	40	++	0.0.0.0	0011100000
7	21	Generalized	65 days	None	+++	3	+	0.0.0.0	0001100000
8	43	Asymptomatic	24 years	Yes	+++	9	+	0.0.0.0	0011100000

diminished superficial reflexes, and 1 case had an absent bulbo-cavernosus reflex. Three had slightly increased knee jerks, 1 had a positive Gordon reflex, and 2 had a positive Oppenheim. Three cases had a Romberg, 4 cases were incoordinated, 3 cases had tremor, and 1 had an ataxic gait. There was a disturbance of sensation in 1 case. One case had mental symptoms. Two cases gave a mild reaction after lumbar puncture.

PATHOLOGY

The factors concerned in the production of the colloidal gold reaction in the cerebrospinal fluid are not yet determined. It is presumed to be due to the presence of a globulin substance but which does not seem to be the same as that which produces the ordinary globulin reaction. Many conditions may give a curve in the colloidal gold reaction in the cerebrospinal fluid but cerebrospinal syphilis of a moderately advanced stage usually gives a typical reaction 0012231000. The reactions in this series of cases do not approach this typical cerebrospinal syphilitic curve except in one case. It seems probable, however, that the slight reactions shown in the table are the precursors of what would later be a cerebrospinal syphilitic curve. Though in only 2 cases is there a pleocytosis yet the large proportion that show slight neurologic findings and the presence of an increased globulin in every case make us view this series with grave suspicion. It seems probable that even slight positivity of the colloidal gold curve, whether the other reactions of the fluid are pathologic or not, is fairly strong presumptive evidence that these cases have a spirochetal infection of the nervous system. We consider that every such case should be observed with the minutest care and measures taken to saturate the entire body with antisyphilitic remedies for the purpose of controlling the syphilitic infection as rapidly as possible.

TREATMENT

If a case shows no clinical neurologic signs and the fluid reaction has a normal cell count, a slightly increased globulin, a negative Wassermann and a very slight colloidal gold reaction such as: 0001100000, intensive treatment should be instituted with examinations of the cerebrospinal fluid four times a year. Should there

be a gradual decrease in the globulin and colloidal gold until a negative reaction is obtained systemic treatment may be all that is necessary for this condition, but we would advise that at some period during the course of treatment a provocative intraspinal injection of 0.2 mg. dosage of salvarsanized serum should be given and the cerebrospinal fluid examined a week later. Should this be negative no further intraspinal therapy should be administered but should it show an increase in pathologic findings we consider it advisable to commence intraspinal treatment.

Should there be neurologic signs present, of a nature sufficient to indicate an incipient neurosyphilis, or should there be a pleocytosis in the fluid, it is reasonable to suppose that the case has advanced to the stage where the most intensive treatment is necessary and we would advise that combined systemic and intraspinal therapy be adopted. The course should be the same as that detailed for the preceding class.

Class F.—(Table VIII).—Significance of the reaction. Cells normal or increased, globulin normal or increased, Wassermann positive, colloidal gold negative or positive.

SUMMARY

There were 34 cases belonging to this class. Twelve were generalized syphilis, 4 were late syphilis, and 18 were asymptomatic syphilis. In 2 cases primary sores were present. In 5 cases there was no evidence of a primary sore on the genitals ever having been present. The skin in 21 cases was negative, 2 cases had a macular rash, 5 had a maculopapular rash, 2 had secondary syphilides, 1 had a papular rash, 2 had gummata and 1 had rupia. The mucous membranes in 20 cases were negative, 10 had mucous patches, and 2 had condylomata about the anus. Two cases had syphilis of the bladder. Three had specific laryngitis, and one had epididymo-orchitis. One case had syphilitic jaundice. Ten cases had bad neurologic family history. All the personal histories as to previous nervous disease or diseases which might result in a weakened nervous system were negative. Fifteen cases did not use alcohol, 5 used it very slightly, 5 slightly, 7 moderately, and 2 to excess. Eleven cases had had previous treatment for their syphilis with salvarsan over a period of 1 to 12 years ago. Six cases had had previous

SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

TABLE VIII
CLASS F. TYPICAL SEROLOGIC FINDING. CELLS NORMAL OR INCREASED. Globulin Normal or Increased.
WASSERMANN POSITIVE. COLLOIDAL GOLD POSITIVE OR NEGATIVE.

CASE NO.	AGE	STAGE OF SYPHILIS	CLINICAL NEUROLOGIC DIAGNOSIS	DURATION OF SYPHILIS	BLOOD WASS'N	CELLS	GLOB-ULIN	SERUM WASS'N	COLLOIDAL GOLD
1	26	Generalized	None	4½ months	+++	47	+++	0.0.0.3	Not done
2	25	Generalized	None	1 year	+++	20	Neg.	0.1.4.4	Not done
3	34	Generalized	None	9 months	+++	17	+	0.0.0.3	Not done
4	22	Generalized	None	8 months	+++	9	+	0.3.4.4	Not done
5	30	Generalized	None	9 months	+++	35	+	1.3.4.4	4433211000
6	23	Generalized	None	2 years	+++	32	+	4.4.4.4	Not done
7	30	Generalized	None	No history	+++	107	+	0.0.3.4	0001000000
8	29	Generalized	None	3 months	+++	32	+	0.0.0.2	0001100000
9	31	Generalized	None	15 months	+++	4	Neg.	0.0.2.3	Not done
10	23	Generalized	None	1 year	+++	24	+	0.0.2.4	Not done
11	39	Generalized	None	1 month	+++	4	+	0.0.3.4	Not done
12	28	Generalized	None	3 years	+++	12	+	4.4.4.4	Not done
13	33	Late	Tables	No history	+++	90	+	4.4.4.4	Not done
14	50	Late	Tables	No history	+++	13	+++	4.4.4.4	Not done
15	28	Late	Tables	8 years	Neg.	196	+++	0.4.4.4	Not done
16	31	Late	None	No history	+++	2	Neg.	0.0.0.4	Not done
17	31	Asymptomatic	Cerebrospinal	11 years	+++	36	+++	0.4.4.4	Not done
18	43	Asymptomatic	Tables	12 years	+++	57	+	1.4.4.4	2223320000
19	41	Asymptomatic	Tables	No history	+++	123	+	4.4.4.4	3212210000
20	34	Asymptomatic	Tables	12 years	+	18	+	4.4.4.4	1222210000
21	38	Asymptomatic	Tables	No history	+	120	+	4.4.4.4	0012321100
22	36	Asymptomatic	Cerebrospinal	10 years	+++	29	+++	0.0.0.4	Not done
23	32	Asymptomatic	Cerebrospinal	4 months	Neg.	17	+	0.0.0.4	Not done
24	28	Asymptomatic	None	No history	+++	13	+	0.0.4.4	Not done
25	25	Asymptomatic	None	9 years	+++	13	Neg.	3.4.4.4	Not done
26	49	Asymptomatic	Tables	24 years	Neg.	30	+	2.4.4.4	Not done
27	30	Asymptomatic	Tables	8 years	+++	28	+	4.4.4.4	Not done
28	24	Asymptomatic	None	2 years	+++	63	+	4.4.4.4	Not done
29	23	Asymptomatic	None	3 years	+++	142	+	4.4.4.4	2233210000
30	44	Asymptomatic	Paresis	8 years	+++	38	+	1.4.4.4	Not done
31	31	Asymptomatic	Paresis	5 years	+	25	+	1.4.4.4	Not done
32	30	Asymptomatic	None	4½ years	+	9	+	3.4.4.4	Not done
33	32	Asymptomatic	None	12 years	+	13	+	0.4.4.4	Not done
34	33	Asymptomatic	None	2 years	++		+		

mercurial treatment. The average duration of the syphilis was $7\frac{1}{4}$ years. Seven cases gave no history of syphilis.

Nineteen cases gave a history of symptoms indicating cerebro-spinal involvement. The onset of symptoms was sudden in four cases. In one case the onset was severe, characterized by epileptiform seizures. The symptoms of onset may be tabulated as follows in the order of their frequency:

Disturbances of vision	5 cases.
Bladder symptoms	4 cases.
Mental deterioration	4 cases.
Disturbances of hearing	3 cases.
Headaches	2 cases.
Nervousness	2 cases.
Lightning pains	2 cases.
Rombergism	2 cases.
Convulsions	1 case.
Hemoplegia	1 case.
Neuritis	1 case.
Syncope	1 case.

The average period between the contraction of the syphilis and the onset of symptoms was $5\frac{3}{4}$ years. The average duration of the symptoms was 4.5 years.

Cranial nerves.	Normal	Sl. Pathologic	Pathologic
I.	32	2	0
II.	31	3	0
III, IV, VI.	27	2	5
VII.	30	2	2
VIII.	33	1	0
Reflexes. No. of cases.	Normal	Sl. Pathologic	Pathologic
Superficial	29	1	4
Deep reflexes of arm	26	4	4
Knee jerks	17	10	7
Achilles jerk	25	2	7
Babinski	31	3	0
Romberg	21	7	6
Incoordination	24	8	2
Pupils			
Equality	28	6	0
Regularity	32	0	2
Accommodation	32	0	2
Light	28	0	6
Tremor	29	0	5
Gait	29	0	5

Of this series seven cases were advanced tabes, three cases were advanced cerebrospinal syphilis and two cases were moderately advanced paresis. The following table will give the number of cases showing alteration in the more important cranial nerves and reflexes. (Pathologic may be understood to be a marked alteration in the function of the cranial nerve, or a marked alteration, either an increase or diminution in the reflex. Slightly pathologic may be understood to be only a slight alteration of the function of the cranial nerve or in the reflex.)

The most frequent sensory finding was a diminution in the pain sense. Cases of frank tabes generally had an area of anesthesia or of hypesthesia to light touch over the lower part of the ribs. Abnormal sensory findings were present in over a third of the cases. Five cases complained of reaction after lumbar puncture, in three it was slight and in two it was severe, with headache and faintness.

PATHOLOGY

In this class, as in all other classes, the question for consideration is whether the *Spirocheta pallida* are present in the central nervous system or not. Already the conclusion has been arrived at that an increased cell count, or an increased cell count and an increased globulin, or a positive colloidal gold are indications of the presence of the organism despite whether the Wassermann is positive or negative. We would consider, therefore, that cases giving these types of serology are cases of neurosyphilis and the *Spirocheta pallida* is present in the central nervous system.

In cases, however, in which we get the fluid finding of: cells not increased, globulin not increased, Wassermann positive, colloidal gold negative, and blood Wassermann positive, or in which we get the fluid finding of: cells not increased, globulin increased, Wassermann positive, colloidal gold negative, and blood Wassermann positive, if no neurologic signs are present we may have another condition with which to deal. It is a known fact that the blood Wassermann of a neurosyphilitic with a positive Wassermann in the cerebrospinal fluid, may be kept positive by the absorption into the general circulation of the reagin from the cerebrospinal fluid. It has not been thought possible, however, for reagin to pass from the general circulation through the filter of the choroid

plexus into the cerebrospinal fluid. To determine whether bodies of the nature of reagin could pass the chorioid plexus, we have examined the cerebrospinal fluid of a few cases of gonorrhea in which the gonorrheal complement-fixation test was positive in the blood. In the majority of cases in which the fixation was positive in the blood the same amount of positivity was also found in the cerebrospinal fluid. Though our series of cases is not yet large enough to warrant publication or even to draw positive deductions from, it is an illuminating point that if the antibody which takes part in the gonorrheal complement-fixation reaction can pass into the spinal fluid without the organism itself being present, there seems no reason why the reagin of the Wassermann reaction can not also pass the same way, particularly if there is damage to the chorioid plexus. It is this fact which makes us largely of the opinion also that a slight excess of globulin is produced in the same way. Therefore, in early cases of syphilis in which the blood Wassermann is strongly positive and in which neurologic signs are absent, a positive Wassermann or a positive globulin finding alone in the cerebrospinal fluid does not seem to warrant the assumption that the *Spironema pallida* is present in the central nervous system. A strongly positive Wassermann in the fluid, or a more strongly positive Wassermann in the fluid than in the blood, make us assume, however, in the present stage of our knowledge that the *Spironema pallida* is probably present. All cases with a positive Wassermann or a positive globulin should be viewed with grave suspicion, but unless there are other indications intraspinal treatment need not be administered immediately.

TREATMENT

In considering the treatment in this type of case it is well to divide the cases into two classes. First, those without any clinical neurologic signs, second, those in which clinical neurologic signs are present. We will consider the former class first. Cases without neurologic signs are evidently earlier than those in which signs are present, the damage to the tissues is not gross and the probability of effecting a permanent cure without leaving lesions, which are the result of scar formation, is greater. When the fluid finding in this type of case is cells not increased, globulin not increased, Wassermann positive, colloidal gold negative, there is no definite

indication for considering the *Spironema pallida* present, but such case should be regarded with grave suspicion. The case should be continued on intensive systemic treatment and a second lumbar puncture done in between two and three months. If the Wassermann is then negative the systemic treatment should be continued with half yearly examinations of the cerebrospinal fluid, and if it remains negative no other treatment need be adopted. Should the Wassermann become more strongly positive, remain stationary, or become negative and later positive, intraspinal treatment should be adopted. Before the inception of intraspinal treatment, however, it would be well to give one provocative injection. The course of intraspinal treatment in these cases should consist of ten injections at ten day intervals. If the Wassermann falls quickly to negative a less number of treatments may be given. The fluid should be examined half yearly for at least the next three years. If it remains negative the case may be considered permanently arrested. If it should become positive further intraspinal treatment should be given. If, at any time, the cerebrospinal fluid finding should show a change to another type treatment for that type should be adopted.

In the treatment of cases that give the serologic finding: Cells normal, globulin increased, Wassermann positive, colloidal gold negative, the same line of treatment should be followed. One case may be cited illustrating the results of systemic treatment in this class of case:

Pte. D. Age 28. Admitted with asymptomatic syphilis. Patient gave no history of syphilis, but complained of failing memory and headache. There were no neurologic signs. He had had no previous treatment. Blood Wassermann strongly positive. Cerebrospinal fluid: Cells seven, globulin ++, Wassermann 0.0.0.4. He received seven injections of salvarsan and a second lumbar puncture was done. Serologic finding: Cells 1, globulin negative, Wassermann negative.

In those cases in which the serologic finding is cells increased, globulin increased, Wassermann positive, colloidal gold negative, or the finding cells normal or increased, globulin normal or increased, Wassermann positive, colloidal gold positive, we are dealing with unquestionable neurosyphilis, i. e., a spirochetal invasion of the nervous tissues. This type of case should receive intensive systemic treatment combined with intraspinal treatment. We would advise for these cases a course of intraspinal treatment of ten in-

jections at ten day intervals, the dosage being that which has been previously stated. We do not consider it advisable to give this type of case less than eight injections, despite the rapidity with which the cerebrospinal fluid may become negative. Should the fluid be negative at the completion of this course of treatment half yearly examinations should be made over three or four years and a final one two years after completion of systemic treatment. Should the fluid still be positive at the completion of the first course and no neurologic signs have developed, he should receive six months rest from intraspinal treatment and then be placed on a second course. If the fluid should then still be positive another six months rest period should be given followed by a third course. If at the completion of the first course the fluid is still positive and neurologic signs have developed, treatment should be continued as for that type of neurosyphilis which is indicated clinically. If the fluid is negative at the end of the first course, but subsequently becomes positive, a second course of intraspinal treatment should be given.

In the second subdivision of this group the diagnosis has to be made neurologically between cerebrospinal syphilis, tabes dorsalis, and paresis. In the case of cerebrospinal syphilis we have an earlier stage of the disease and one more amenable to treatment than either tabes or paresis. As degenerative lesions have occurred with destruction of the neurones we can not expect by antisiphilitic treatment alone to cure the deformities. Proper neurologic treatment should be given, but in some cases the deformity will persist throughout life. The treatment should be combined systemic and intraspinal. The course of intraspinal treatment should be that recommended for the class of cases with positive cerebrospinal fluid findings and negative clinical neurologic findings. More courses of treatment will probably be required and the treatment should be continued until the four reactions in the cerebrospinal fluid are normal.

TABES

Neurosyphilis is, in its early stages, an irritative process, but later becomes degenerative. When the degenerative process is greatest in the cord the symptoms of tabes predominate. Cases of tabes are probably of two types. First, those in which the degeneration is a result of the activity of the *Spironema pallida* itself, and

second, those in which the degeneration is secondary to previous activity of the organism. The latter type comprises only a small percentage of the cases of tabes. The cerebrospinal fluid is usually negative and the process itself may be either stationary or progressive. Intraspinial treatment unavailing. In the stationary type re-educative methods to open new pathways to replace those destroyed are valuable. The progressive type is incurable by our present methods.

The tabes resulting from the active presence of the *Spironema pallida* is more amenable to treatment. It is necessary to have three things in view in the management of these cases. First, that the *Spironema pallida* are actively present in the tissues of the central nervous system and treatment must be instituted for their eradication. Second, that already neurones have degenerated and new pathways must be made and other neurones trained to take the place of those which have been destroyed. Third, in the vast majority of cases the syphilis is not entirely limited to the central nervous system, but is a systemic syphilis as well, and so systemic treatment must be carried on at the same time.

There are grave dangers associated with each one of these methods of treatment. On account of the *Spironema pallida* being present among the already damaged neurones, the treatment for their eradication should not be too strenuous, for if a large number of the organisms are destroyed at one time the liberated syphilo-toxins may overwhelm the weakened neurones and precipitate symptoms which, unfortunately, are permanent in many cases. It is therefore inadvisable to institute intraspinal treatment at once in a case of tabes with clinical neurologic signs as the following case will illustrate:

Pte. T. Age 39. Admitted with clinical tabes. Syphilis was contracted seventeen years ago, for which he had received some treatment. While on service in France, one year previous to admission here, he developed a tabetic gait, weakness of the muscles of the legs, ataxia, incoordination and loss of bladder control. Previous to admission to this hospital he had received some intravenous salvarsan. On admission he complained of girdle sensations, lightning pains, and incontinence. The cilio-spinal reflex was absent. The superficial reflexes were all sluggish and the deep reflexes of the arms and legs were absent. There was marked incoordination and Romberg. The pupils were unequal and were of the Argyll Robertson type. The gait was tabetic. The sense of joint position was fair. There was a band of anesthesia encircling the chest extending from the

fifth rib to the costal margins. There was diminution of the pain sense. He had slight loss of bladder control but was not inconvenienced by this greatly. Blood Wassermann strongly positive. Cerebrospinal fluid: Cells 3, globulin +, Wassermann 0.4.4.4.

He was placed on intraspinal treatment immediately and received 3 injections of 0.2 mg. arsenolized serum at eight day intervals. After the third injection he became much worse; completely lost the use of his legs, the control of his bladder and rectum and suffered from severe root pains. He continued in this condition for several months and then slowly improved. After his clinical signs had abated sufficiently he was again placed on more careful intraspinal treatment, which resulted in his cerebrospinal fluid becoming nearly negative and his neurologic signs improving.

Had this case remained untreated for much longer he would probably have become eventually one of the cases of clinical tabes without a pathologic cerebrospinal fluid. A sufficient number of organisms were actively present still in the central nervous system to allow treatment to liberate such an amount of syphilo-toxin as to produce severe damage to the neurones and a fatal result might have been obtained. Consequently, in cases of tabes we are strongly of the opinion that intraspinal treatment should not be instituted at once.

It has been proved that arsenic will pass from the blood to the cerebrospinal fluid normally and in greater quantities if the amount of the cerebrospinal fluid is reduced. It is better then to start the treatment of tabetics with intravenous injections of salvarsan. After two or three injections a certain amount of arsenic has passed into the fluid and destroyed a few of the organisms without the liberation of too great an amount of syphilo-toxin. To gradually increase the amount of arsenic which passes over, it is well, after the third or fourth intravenous injection, to withdraw about 15 or 20 c.c. of cerebrospinal fluid every two weeks. By the time seven injections have been given, the number of *Spironema pallida* have been materially reduced and the tissues accustomed to the liberation of gradually increasing amounts of syphilo-toxin. When this has been done intraspinal treatment should be instituted. The dosage should be commenced with 0.2 mg. and be very gradually increased. The course should consist of twelve injections. If the fluid should be positive at the completion of this course we would

advise a rest of six months followed by a second course. In this way the treatment may be carried on as long as necessary. The results neurologically are dependent upon the amount of nervous tissue already destroyed. If the process is largely an irritative one the signs may completely disappear. The results of degeneration are not improved by this treatment.

Intravenous treatment should also be given with great care. Tabetics are usually in poor physical condition and can not stand massive doses of salvarsan. The doses therefore should be small and be given at least at weekly intervals. Reeducative methods should not be instituted immediately but it is well to wait until half the first course of intraspinal treatment has been given before their inception.

When a case of neurologic tabes with a type serology of—cells increased, globulin increased, Wassermann positive, colloidal gold negative or showing the tabetic curve 1.2.2.2.2.1.0.0.0.0. comes for treatment the method that we would adopt is as follows: The case should be placed on systemic treatment of a careful nature, preferably 0.3 grams of salvarsan and 1 grain of mercury at weekly intervals. After the third injection of salvarsan 15 to 20 c.c. of cerebrospinal fluid should be withdrawn. This is to be repeated at fourteen day intervals for three drainages. Two weeks after the last drainage the patient should receive 0.2 mg. salvarsanized serum intraspinally. If the reaction is very mild the interval between the injections may be made one to fourteen days. If the reaction is severe there should be a three week interval. For the first three injections the patient should receive 0.2 mg., for the next three 0.3 mg., for the next three 0.4 mg., and for the last three 0.5 mg. Should the reaction be severe an 0.2 mg. dosage should be given throughout. The most important indication for dosage and time interval is the reaction, but a neurologic examination should be made before each treatment. If the reactions are mild but the neurologic findings are retrogressing it is well to use only a 0.2 mg. dosage throughout. Serologic improvement is usually slow. The cell count is the first to lessen, but has a tendency to fluctuate. Subsequent increases of cell count do not, however, reach the number found after the provocative effect of the first injection and each fluctuation is less than the preceding. The globulin is very resistant to treatment and may remain permanently increased. The Wassermann

falls slowly to negative. The colloidal gold is resistant but after sufficient treatment it also becomes negative. A typical case may be cited to illustrate the effect of treatment in tabetics:

Pte. M. Age 38. Admitted with tabes. Patient gave no history of syphilis nor was there any indication of previous syphilitic lesions. Two years ago he developed symptoms of neuritis in the left arm. Six months previous to admission he had double vision. On admission he complained of lightning pains in the legs. There was ptosis of the right lid and paresis of the right external rectus. The ciliospinal reflex was absent. The superficial reflexes were increased. The deep reflexes were absent and there was a marked Romberg and incoordination. The pupils were unequal and of the Argyll Robertson type. There was a slight tremor, a tabetic gait, a poor sense of joint position and a general diminution of sensation for pain. There was an area of anesthesia between the fourth and seventh ribs on the left side of the chest. Blood Wassermann positive. Cerebrospinal fluid: Cells 120, globulin ++, Wassermann 4.4.4.4. Colloidal gold 0012321100.

- 5/11/18 Admitted to hospital. Placed on .45 grams novarsenobillon at weekly intervals.
- 18/11/18 Removal of 15 c.c. cerebrospinal fluid.
- 5/12/18 Removal of 15 c.c. cerebrospinal fluid.
C.S.F. Cells 26, globulin +, Wassermann 0.4.4.4.
Colloidal gold 0111100000.
- 19/12/18 Removal of 15 c.c. cerebrospinal fluid.
C.S.F. Cells 18, globulin ++, Wassermann 1.4.4.4.
Colloidal gold 3322110000.
- 6/ 1/19 0.2 mg. Arsenolized serum intraspinally.
- 23/ 1/19 0.2 mg. Arsenolized serum intraspinally.
- 6/ 2/19 0.2 mg. Arsenolized serum intraspinally.
- 20/ 2/19 0.3 mg. Arsenolized serum intraspinally.
C.S.F. Wassermann 0.1.4.4.
- 4/ 3/19 0.3 mg. Arsenolized serum intraspinally.
C.S.F. Cells 17, globulin +, Wassermann 0.0.4.4.
- 20/ 3/19 0.3 mg. Arsenolized serum intraspinally.
C.S.F. Cells 22, globulin +, Wassermann 0.0.0.4.
- 2/ 4/19 0.4 mg. Arsenolized serum intraspinally.
C.S.F. Cells 35, globulin ++, Wassermann 0.1.4.4.
- 18/ 4/19 0.4 mg. Arsenolized serum intraspinally.
C.S.F. Cells 11, globulin +, Wassermann 0.0.3.4.
Colloidal gold 0001000000.

Neurologically, the superficial reflexes became almost normal, the deep reflexes in the arms were all present, the knee jerks and Achilles jerks were still absent, there was a very slight Romberg and no incoordination. The tremor, gait, sensations, and the conditions of the pupils were unchanged.

We do not consider this case to be cured but we believe with further treatment the cerebrospinal fluid will become negative, although the neurologic signs may not improve further than they are at present.

PARESIS

A sufficient number of cases of paresis have not passed through our hands at this hospital to make it advisable for us to detail the method of treatment to be adopted in this condition. Suffice it to say that we believe that clinical paresis should be treated in an entirely different manner from clinical tabes. Intraspinial treatment should be instituted at once and combined with intravenous treatment in order that the paretic may be saturated with anti-syphilitic remedies by every avenue at our disposal. Treatment should be continued over a much longer period without a rest interval. If the patient is in good physical condition the treatment should be continued until the cerebrospinal fluid is negative or until neurologic and serologic findings show by retrogression that treatment is useless. If the case is improving and a rest interval is instituted the deterioration that takes place during this interval is so rapid and widespread that further treatment is of no avail. Previous experience has taught us that in early paretics, either those who are asymptomatic and whose colloidal gold curve is a typical paretic one, 5544332100, or those in which the clinical signs are commencing, intraspinal treatment is of great value and holds out the best method of producing a prolonged and possibly permanent remission. In 25 per cent of cases of advanced paresis, intraspinal treatment is undoubtedly of value, but in the remainder any treatment whatsoever is unavailing.

We are unable at present to state our opinion concerning the definite significance of the colloidal gold reaction. Unfortunately the pressure of routine work on the staff of the laboratory has been so great that they were unable to perform this reaction on the majority of our fluids.

There are two very important questions in connection with the subject of neurosyphilis that are not yet answered. One is, whether a generalized syphilitic with a negative cerebrospinal fluid, if kept on proper systemic treatment, will ever develop a positive fluid or will ever show clinical neurosyphilis. The other is whether a neuro-

syphilitic, whose fluid has been made negative by treatment, will ever suffer from a recurrence, either of the positivity of the fluid or of clinical signs. The answer to these queries is still theoretical for little is definitely known. The only method to ascertain the truth in connection with the progress of these cases, either with or without treatment, is to keep a large number under close observation clinically and serologically throughout their lifetime. Therefore, we can not impress too strongly on the government and the profession of Canada, in view of the national importance of the question and the unparalleled opportunities that the present time offers, the necessity that such a series of cases as we have here been reviewing be kept under observation throughout the lifetime of each patient in order that many doubtful points may be made clear by the light of future events.

We are also strongly desirous of impressing upon the government the necessity that all cases of neurosyphilis, which have occurred in the army, should be kept under close observation and efficiently treated in order that they may not become a charge on the state at some later date through the ravages of paresis or tabes.

CONCLUSIONS

1. The *Spironema pallida* invade the central nervous system during the early part of the stage of generalization of syphilis.

2. On account of the great damage done by the *Spironema pallida* to the central nervous system, if treatment of a neurosyphilitic is delayed, a proper diagnosis should be made and treatment instituted at the earliest possible date, viz., before clinical signs appear.

3. The only certain method of making this diagnosis when it will be of most value to the patient, is by performing a lumbar puncture and examining the cerebrospinal fluid. A lumbar puncture should be done on every case of generalized, late and asymptomatic syphilis, on every case of primary syphilis with a positive blood Wassermann, and on every case of nervous disease, coming for treatment. There is no reason why a lumbar puncture can not be done in ordinary office practice.

4. If the serology does not indicate the presence of the *Spironema pallida* we do not advise treatment directed with special attention to the nervous system. We do not consider that the following find-

ings in the cerebrospinal fluid indicate an invasion of the *Spirocheta pallida* in an early case of syphilis without neurologic signs:

(a) Cells 0 to 7. Globulin not increased. Wassermann negative. Colloidal gold negative.

(b) Cells 0 to 7. Globulin increased. Wassermann negative. Colloidal gold negative.

(c) Cells 0 to 7. Globulin normal or increased. Wassermann positive. Colloidal gold negative.

These cases should be watched with the greatest of care but unless further indications appear at a later date no other treatment than systemic is necessary.

5. If the serology does indicate invasion of the central nervous system by the *Spirocheta pallida* we advise special treatment for the condition of the nervous system. We consider the following serology findings to indicate neurosyphilis, even though clinical neurologic findings are negative:

(a) Cells increased over seven. Globulin not increased. Wassermann negative. Colloidal gold negative.

(b) Cells increased over seven. Globulin increased. Wassermann negative. Colloidal gold negative.

(c) Cells increased. Globulin normal or increased. Wassermann positive. Colloidal gold negative or positive.

6. All cases of generalized, late or asymptomatic syphilis should have a neurologic examination, for in a few cases of late degenerative neurosyphilis the clinical findings are positive but serologic findings are negative. Neurologic findings are a guide to the treatment to be adopted.

7. If the stage of invasion by the *Spirocheta pallida* is early systemic treatment may be all that is necessary. If the stage of invasion is later or if neurologic signs are present combined systemic and intraspinal treatment are a necessity.

8. Ogilvie's modification of the Swift-Ellis method is the most advantageous for the preparation of salvarsanized serum. There is no reason why intraspinal treatment can not be given in ordinary office practice.

9. In cases of tabes with marked clinical signs caution should be used in commencing intraspinal treatment on account of dangerous precipitation of symptoms.

ACKNOWLEDGEMENTS

We desire to express our appreciation of the encouragement given and the assistance rendered by us by Colonel W. T. M. MacKinnon, C.M.G., Officer Commanding this hospital, and of the assistance rendered by Major V. N. MacKay and the staff of the laboratory, and by the staff of the syphilis service of this hospital, particularly by Sergeant H. C. Brown.

KEY TO TABLES

In the accompanying tables the undermentioned methods were used to examine the cerebrospinal fluid for each of the four reactions:

Cells. By the Turck Counting Chamber.

Globulin. A ring test with a saturated solution of ammonium sulphate.

Wassermann. Five tubes were set up, one of which was used as a control. To the first tube the same amount of cerebrospinal fluid was added as the amount of serum used in doing the ordinary blood Wassermann. To the second tube twice the amount used in the first tube was added. To the third tube twice the amount of cerebrospinal fluid used in the second tube and to the fourth tube twice the amount used in the third. To the control tube, which did not contain antigen, twice as much cerebrospinal fluid as was used in the fourth was added. In reporting the results each figure of the report indicates one of the four tubes. If in any tube there is 100 per cent inhibition of hemolysis it is reported as 4, if 75 per cent as 3, if 50 per cent as 2, if 25 per cent as 1. If no inhibition of hemolysis, it is reported as 0.

Colloidal Gold. Done by the ordinary technic.

REFERENCES

- ¹MacRobert, R. B.: Cause of Lumbar Puncture Headache, Jour. Am. Med. Assn., May 11, 1918, lxx, No. 19, p. 1350.
- ²Ogilvie: Intraspinal Treatment of Central Nervous System with Salvarsanized Serum of Standard Strength, Jour. Am. Med. Assoc., November 28, 1914, lxiii, 1936.

THE MEDICAL AND SOCIAL CARE OF SYPHILIS AT THE WASHINGTON UNIVERSITY DISPENSARY*

BY RICHARD S. WEISS, M.D., AND ADOLPH H. CONRAD, M.D.,
ST. LOUIS, MO.

(Received for publication, February 1, 1920)

THE routine treatment of syphilis in a large dispensary depends for its efficiency upon three factors, all of them being, perhaps, of equal importance. These factors are: first, the aspect of the problem from the public health standpoint; second, the reaction of the patient and his family to the measures used for their own protection, health, and comfort; third, the clinical results of treatment.

In all of the work done by this clinic and its staff, the first point has been considered the one which was to be kept foremost in mind and that, while social service work and medical treatment were of the utmost importance, the prevention of the spread of syphilitic infection was the chief consideration and not the serological cure of individuals.

With such ideas, naturally it is to be expected that the routine of the clinic would be so arranged that the stamping out of individual "foci of infection" be the first consideration. We do not believe that the spread of syphilis can be checked by education, by religion, or by reform movements alone, although we admit that these efforts may be of great assistance, especially education. It is our belief that far more would be accomplished if every individual with communicable syphilis were rendered no longer a menace to others. We do not believe that education, religion, and reform movements can in the least alter the primitive sexual passions implanted in man which are responsible for the communication of syphilis in a large majority of cases.

The entire problem should be viewed from a wide angle and the welfare of all must be considered before the welfare of the individual. With this thought before us, we can concretely express our belief in a few words.

*From the department of dermatology, Washington University School of Medicine, service of M. F. Engman, M.D., and W. H. Mook, M.D.

If every individual who has acute infectious syphilis be given two doses of arsphenamine within one week, the effect on the morbidity rate of this disease would be tremendous, and, if this program were kept up, within a measurable period of time the spread of this disease would be largely under control.

Education plays its share in this program. If the individual can be taught what syphilis is, what it does, and what its remote

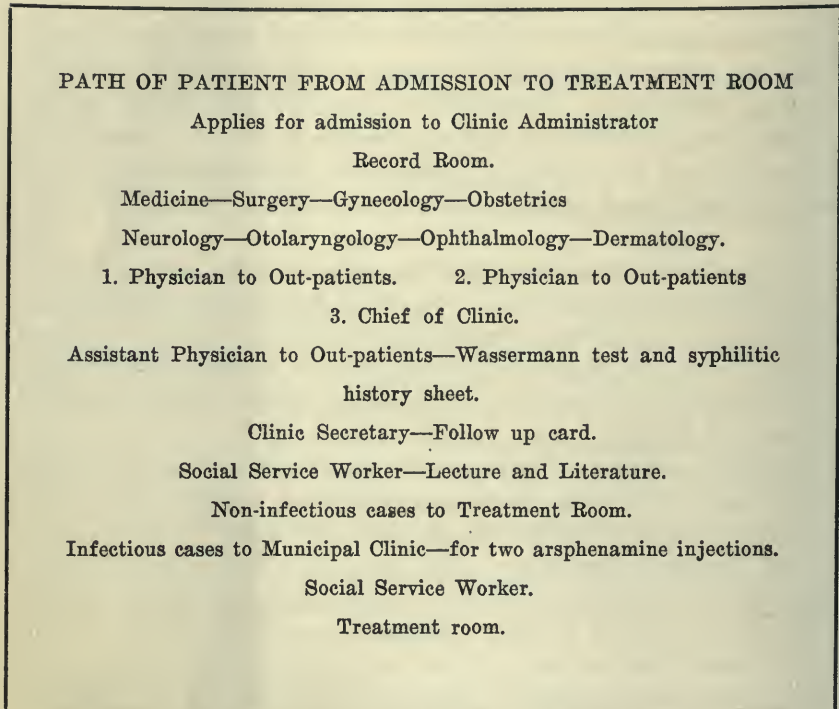


Fig. 1.—Path of patient from admission to treatment room.

effects are, the responsible element of the population will seek the sterilizing treatment and will be convinced of the necessity for prolonged care; the "irresponsibles" must be forced to take the treatment which will make them no longer a menace to others. This educational work is now being carried out by the U. S. Public Health Service and other agencies, and facilities for the treatment end of the work are being gradually introduced. Stimulated by federal appropriations which are available in each state when its

legislature shall have appropriated an equal amount of money, free clinics are being established all over the country.

The St. Louis Health Department, through the efforts of Dr. M. F. Engman, is now carrying out the sterilizing program.* Any individual with communicable syphilis is given two injections of arsphenamine free of charge (see Appendix F), and if the depart-

O.P.D. Form 6

Washington University Dispensary

Out-Patient Department
of
Barnes Hospital and St. Louis Children's Hospital

Name James Smith.

No. A21348 Date April 1, 1916.

Dermatology

**Always bring this Card with you
Only for patients unable to pay a physician's fee**

Fig. 2.—Admission card. Color, blue. Printed on flexible linen.

ment is notified of any infectious case that is not being treated, it has the power to subject those cases to treatment and does so.

CLINIC ROUTINE

The work of the social service and medical staff of our organization is so closely knit together that it will perhaps be better to give a general description of the clinic routine and later enlarge upon the details.

*The words "sterilizing program" used in this connection mean making the syphilitic noninfectious, and have no reference to operative measures for the prevention of conception.

O. P. D. Form 1		
Name	James Smith	Age 28
Address	1463 S. Third St.	Sex M
Date	April 1, 1916	S. M. W.
		OCCUPATION Laborer BIRTHPLACE Ala

WASHINGTON UNIVERSITY DISPENSARY. No. A21348.

Out-Patient Department of Barnes Hospital and St. Louis Children's Hospital

DERMATOLOGY

DIAGNOSIS: (To be filled out after the first visit.)

Syphilis, early.

Patient Examined by Weiss

Patient stated that he had a chancre in Feb. 1916 for which he was given local treatment only.

For the past 10 days he has had a general eruption.

He presents a general maculo-papular eruption, slightly infiltrated, coppery colored, thickly distributed over the trunk where it follows the cleavage lines of the skin.

Numerous mucous patches in the mouth. Healing penile ulcer.

Take blood for Wassermann.

Send to Municipal Clinic.

Fig. 3.—General history sheet.

O P D. Form 1A

Name James Smith Age 28
 Address 1463 S. Third St. Sex M
 Date Apr. 1, 1916. S. 1 1

OCCUPATION
Laborer
 BIRTHPLACE
Ala.

WASHINGTON UNIVERSITY DISPENSARY. No.

Out-Patient Department of Barnes Hospital and St. Louis Children's Hospital

DERMATOLOGY:

Acquired—Hereditary.

Patient examined by Coleman.

Indicate Study (Stamp)

When infected Feb. 1916 Source of infection ProstituteLocation of initial lesion Penis. Wassermann (+ -).Treatment: Dihs Local. (how long taken) Rubs 0 Salvarsan 0Given by Advertising doctor 0 Family doctor YesDispensary 0Anyone else infected: Child 0 wife—husband 0 sister 0brother 0 mistress 0 friend 0 RemarksPresent lesion—early yes late latent Wassermann +++Diagnosis of referring clinic 0Are there any infectious lesions at present? yes If so, where? Mouth and bodyWife—husband healthy? Single How many children living? 0Health of living children? 0Final disposition Refer to Municipal Clinic - then regular treatment.

TREATMENT:

1916	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Hg.	S.
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	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31		

Fig. 4.—Syphilis history sheet (front). Key: W=Wassermann test; S⁶=six decigrams of arsphenamine; numerals=intragluteal mercury injections; column headed "Hg"=number of mercury injections each month and grand total; column headed "S"=number of arsphenamine injections each month and grand total.

FAMILY HISTORY:

Negative

PAST HISTORY:

Usual diseases of childhood. Gonorrhea 1913,
no complications.

PRESENT HISTORY:

Chancere in February followed by
present eruption.Habits Bowels regular. Coffee to excess. Alcohol Sporadic drinker.Were you drinking when infected? YesInitial lesion—Induration: marked, very marked, slight healingLocation (define exactly) Sulcus between foreskin & glans at
prepuce.

ERUPTION:

EARLY		LATE	
Forms	Varieties	Forms	Varieties
MACULAR (Maculo-Papular)	Roseolar <u>t</u>	NODULAR	Agminate
	Annular		Circinate
	Vitiligoid		Serpiginous
PAPULAR (Papulo-Pustular)	Miliary	SQUAMOUS	Diffuse
	Lenticular		Circinate
	Discoid		
PUSTULAR	Acuminate	GUMMOUS	Diffuse
	Obtuse		Tuberous
	Ecthymoid		

Throat and mouth (Describe) Mucous patches lips.Genitals Healing chancre.Heart Normal.Vessels Normal.Blood pressure 122/84Eye Normal to external examination.Reflexes Normal.Cutaneous sensations Not tested.Headaches Not marked.Miscarriages 0

NOTE.—The terms disseminate, corymbosae, confluent, squamous, crustaceous, rupial, ulcerative, cicatricial, and various others, may be added as descriptive adjectives.

Fig. 5.—Syphilis history sheet (back).

Fig. 1 shows the path of the syphilitic patient from admission to the treatment room. The Clinic Administrator admits all patients to the dispensary, inquires as to their financial status, refuses admission to those with incomes above a certain standard (see Appendix A), gives them a card (Fig. 2) to that clinic to which their most prominent symptoms point, and sends them to the record room.

The record room stenographers fill out the heading of a history sheet (Fig. 3) and the patient and blank history are then sent to the various clinics, some direct to Dermatology. When syphilis

WASSERMANN REQUEST		Date <u>4/1/16</u>				
Name <u>James Smith</u>	No. <u>A 21348</u>	Age <u>28</u>				
Service <u>Dermatology</u>	Specimen of <u>Blood</u>					
Previous Wassermann <u>0</u>	Date	By				
Present Diagnosis <u>Syphilis early</u>						
Venereal History <u>Gonorrhea 1913 - Chancere Feb. 1916</u>						
Physical Signs of Syphilis <u>Maculo-papular syphiloderma</u>						
Treatment						
<table border="0" style="margin-left: 40px;"> <tr> <td rowspan="3" style="vertical-align: middle;">Result {</td> <td>Luetic Antigen <u>++++</u></td> </tr> <tr> <td>Cholesterin Antigen <u>++++</u></td> </tr> <tr> <td>Noguchi Antigen <u>++++</u></td> </tr> </table>			Result {	Luetic Antigen <u>++++</u>	Cholesterin Antigen <u>++++</u>	Noguchi Antigen <u>++++</u>
Result {	Luetic Antigen <u>++++</u>					
	Cholesterin Antigen <u>++++</u>					
	Noguchi Antigen <u>++++</u>					
Request of <u>Mr. Conrad</u>						
Report by <u>J.P.S. - Wasserman Lab.</u>						

Fig. 6.—Wassermann report record. This is pasted on the back of the general history sheet.

is discovered in any clinic, the patient is transferred to Dermatology for treatment (Appendix B).

All new and transferred patients are first seen by the junior physician to out-patients who makes the diagnosis. The diagnosis is confirmed by the senior physician to out-patients and, if doubt exists, by the chief of the clinic. The patient then goes to an assistant physician who fills out the syphilis history sheet (Figs. 4 and 5), takes blood for a Wassermann test (Fig. 6), and sends the patient to the clinic secretary (Appendix C).

WASHINGTON UNIVERSITY DISPENSARY
Out-Patient Department
of
Barnes Hospital and St. Louis Children's Hospital
No. 16

For_____ *James Smith* _____

Date_____4|1|16_____

1. Your disease is a blood disease caused by a germ carried in the blood, usually requiring about three years of treatment, which can only be cured under the treatment and advice of a physician.
2. Avoid absolutely alcoholic drinks in any form. They counteract the effect of the medicine and hasten the progress of the disease.
3. Avoid smoking. It produces sores in the mouth and renders you more dangerous to others.
4. Kissing is dangerous to others, and if indulged in while you have the slightest sore in the mouth, will almost surely infect them.
5. Be very careful that no person uses your tooth brush, pipe, cigar or cigarette.
6. You must avoid sexual intercourse until you are pronounced cured by your doctor.
7. The course of your disease is determined by a blood test. Your treatment is governed entirely by this test, and many treatments may be required to cure you. The blood should be tested at least once a year and the test must remain negative for five years after your course of treatment has ended before you may consider yourself cured. A yearly test for ten years would be safer.
8. Infection of the wife frequently occurs during pregnancy, and she may present no skin or other symptoms. If the blood test is positive at this time in either husband or wife, the child will probably have the disease.

Fig. 7.—Instructions to syphilitics.

The clinic secretary fills out a "follow-up" card (Fig. 9), and sends the patient with the records to the social service worker. She reads the entire history, fills out the social service record (Figs. 16 and 17) gives the patient Form 16 (Fig. 7), reads it with him, and endeavors to teach him everything he should know about the dis-

WASHINGTON UNIVERSITY DISPENSARY
Out-Patient Department
of
Barnes Hospital and St. Louis Children's Hospital
No. 17

For_____James Smith_____

Date_____4|1|19_____

You are to come to the dispensary on_____April 5th_____at_____1:30
P.M. for an injection of medicine.

Take one tablespoonful of Epsom Salts the night before treatment.

Take no food for three hours before or after the injection except

-----No exceptions-----

You may be required to remain from one to twenty-four hours in the hospital after the injection. Bring a friend or relative to the dispensary with you to see that you get home safely. If permitted to leave within one hour, as in most cases, you are to return home immediately by the shortest route and go to bed at once, remaining for twenty-four hours.

Eight hours after treatment, if you have no fever, have not had a severe chill and are not nauseated, you may take two soft-boiled eggs and a glass of milk. Regular diet may be resumed in twenty-four hours after injection.

Bring this with you to prescription window with _____\$2.50_____.

Fig. 8.—Instructions for arsphenamine injections.

ease. If the patient is infectious, he is sent at once to the Municipal Clinic for two injections of arsphenamine. He is sent back from there to the social service worker. Noninfectious cases and cases returning from the Municipal Clinic are then sent to the treatment room.

MEDICAL TREATMENT

The treatment is carried out under the immediate supervision of the senior assistant physician to out-patients who has two junior assistants.

The standard "course" of treatment consists of three arsphenamine injections one week apart and twenty injections of mercury bichloride* at two to three day intervals, between and following the arsphenamine injections.

This "course" is shown graphically in Fig. 4 which is a reproduction of the history and treatment record of a representative case of early syphilis. The entire record, history, and treatment for two years is available on this card, the total treatment received being clearly shown in the two righthand columns.

The use of this card saves an immense amount of time and labor and it is our belief that no large syphilitic clinic can be efficiently conducted without this, or a similar system.

TREATMENT OF PRIMARY SYPHILIS (APPENDIX D)

Wassermann test.

Course I.

One month rest.

Wassermann test.

Course II.

One month rest.

Wassermann test.

Course III.

One month rest.

Wassermann test.

Then Wassermann tests are made at three months, six months, and one year intervals thereafter. If any one prove positive, and in our experience this is very rare, the whole treatment is gone over again.

TREATMENT OF EARLY SYPHILIS

The same as in primary syphilis but, as the percentage of serological cures is necessarily less, usually more than three courses are given.

*One per cent solution HgCl_2 , 2 per cent NaCl , C. P., in distilled water. Dose: 10 to 20 minims. Potassium iodide is only given to those patients who show evidence of localized syphilitic infiltration.

Name Blank, Bessie Age 29 O. P. D. No. A-20139
 Address 3719 Blank St.
 Dr. _____ Social Worker E.B. Dept. Skin
 Diagnosis Syphilis Early
W.R. 5/1/19 4+
 Notes on Reverse

1919	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
Jan.																																Jan.
Feb.																																Feb.
March																																March
April																																April
May	W	S			X		X	S		X	X	X	S		X	X	X			X	X	X		X	X	X						May
June		X	X		X		X	X	X		X	X	X		X	X																June
July															W																	July
Aug.																																Aug.
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	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	

Fig. 9.—“Follow-up” card. Key: W=Wassermann test; S=Arsphenamine injections; a line from the upper left hand corner of a date square to the lower right hand corner indicates that patient is to return to clinic on that date; when he does return, the line is crossed in the opposite direction.

NIGHT CLINIC FOR WORKING PEOPLE
WASHINGTON UNIVERSITY DISPENSARY
 OUT-PATIENT DEPARTMENT
 BARNES HOSPITAL ST. LOUIS CHILDREN'S HOSPITAL
 EUCLID AND KINGSHIGHWAY

Your Doctor at the Dispensary wants you to return on
if you are not under the care of an outside physician,
 and report to the.....clinic at.....or if
 you cannot come, will you please notify

Date.....

Social Service Dept.

Fig. 10.—“Follow-up” postcard.

TREATMENT OF LATE, LATENT, AND NEUROSYPHILIS

The same as in primary syphilis with the exception that the two preliminary arsphenamine injections are not given and many more than three courses are required.

It has been our experience that many cases who have been treated in the routine manner and who have given persistently positive Wassermann tests are sometimes serologically improved by very mild

No. 1

SOCIAL SERVICE
IN
BARNES HOSPITAL
ST. LOUIS CHILDREN'S HOSPITAL
WASHINGTON UNIVERSITY DISPENSARY

MAINTAINED BY
ST. LOUIS ASSOCIATION FOR SOCIAL WORK

507 S. EUCLID AVE.
ST. LOUIS, MO.
FOREST 7600
STATION 60

Dear Friend:-

Your doctor at the dispensary would appreciate it very much if you would let him know why you have not returned to the Skin Clinic as he advised. Your disease, you know, is a serious blood disease which may affect any and all parts of your body if you do not continue the treatments necessary.

We have received no reply to the postal card sent you some time ago but we hope we will hear from you now. Let us know if you are under the care of a private physician and we will scratch your name from our list.

Yours very truly,

(Miss)

Social Worker.
Skin Clinic.

Fig. 11.—First "follow-up" letter.

treatment. The administration of mixed treatment* by mouth will not infrequently render these cases Wassermann negative.

*By "mixed treatment" is meant either of the two following mixtures:

Mixture No. 1.		
R _x	Mercury bichloride	.1
	Potassium iodide	10.
	Simple syrup q. s. ad.	120.
Mixture No. 2.		
R _x	Mercury bichloride	.2
	Potassium iodide	20.
	Simple syrup q. s. ad.	120.
Dose of each: teaspoonful, t. i. d. p. c.		

SPINAL PUNCTURE

Spinal puncture is done after the second negative Wassermann test. If any positive findings are recorded the case is treated as one of neurosyphilis. *A positive Wassermann in the spinal fluid has the same significance as a positive Wassermann in the blood serum.* Increase in the cell count to ten or more with positive protein tests

No. 2

SOCIAL SERVICE
IN
BARNES HOSPITAL
ST. LOUIS CHILDREN'S HOSPITAL
WASHINGTON UNIVERSITY DISPENSARY

MAINTAINED BY
ST. LOUIS ASSOCIATION FOR SOCIAL WORK

507 S. EUCLID AVE.
ST. LOUIS, MO.
FOREST 7400
STATION 81

Dear Friend:-

We have written you postal cards and have written you letters asking why you have not returned to the Skin Clinio for treatment as the doctor advised, and have had no reply from you. It may be that you do not understand the seriousness of the disease from which you are suffering. You know, it is one which, without treatment, may cause you at any moment to become incapacitated for work and a care to others. It is a disease which you should be worrying about if you are not taking treatments. It is one about which you need not worry if you are persistent in helping the doctor by coming regularly.

I hope you will this time reply to us why you have not been coming to the clinic and why we have not heard from you. It is only for your good that we are writing. Let us know if you are under the care of a private physician and we will scratch your name from our list.

Yours very truly,

(Miss)

Social Worker.
Skin Clinio.

Fig. 12.—Second "follow-up" letter.

are necessary requirements for the case to be considered as neurosyphilis.

GENERAL PHYSICAL EXAMINATION

General physical examinations including urinalysis and blood pressure are made by the medical clinic on all patients before arsenamine is given. Any patient presenting obscure symptoms during treatment is referred to the proper clinic for consultation.

NIGHT CLINIC FOR WORKING PEOPLE

For the past three years funds have been provided by the University for the establishment of a night clinic for working people. This clinic is held twice a week in the dispensary building from 7 to 8 p.m. Only mercury injections are given at this time, the patients having gone through the entire routine of the day clinic before being transferred to the night clinic. They are sent back

No. 3

SOCIAL SERVICE
IN
BARNES HOSPITAL
ST. LOUIS CHILDREN'S HOSPITAL
WASHINGTON UNIVERSITY DISPENSARY

MAINTAINED BY
ST. LOUIS ASSOCIATION FOR SOCIAL WORK

507 S. EXCLUID AVE.
ST. LOUIS, MO.
FOREST 7600
STATION 80

Dear Friend:-

Your doctor at the dispensary would appreciate it if you would let him know why you did not report for the treatment for which you were booked yesterday. He reserved a place for you and I hope you will understand that somebody else might have had your place had we known that you were not coming.

Kindly report to the clinic if you can on

Yours very truly,

(Miss)

Social Worker.
Skin Clinic.

Fig. 13.—Letter sent when patient fails to report for arsphenamine injection.

to the day clinic for arsphenamine and Wassermann tests. This clinic is in charge of the senior assistant physician to out-patients.

SOCIAL SERVICE WORK*

After a diagnosis of syphilis has been made and the "follow-up" card attached by the clinic secretary, the complete history

*The authors are greatly indebted to Miss Elise Boogher, social worker in the skin clinic, for that part of the article which deals with the social service aspect. Appendices C, H, and I, were written by Miss Louise H. Wenzel, A.B., M.A., head of the Social Service, and we wish to express our thanks to her also.

is given to the social worker. It is a great help to have this before her while interviewing the patient, especially in infectious cases.

The social worker tries to impress upon the patient the seriousness of the disease and the treatment required. She sees that the patient understands the necessity for regular and long-continued treatment, designates the days on which treatment is given, and informs him of the cost.

The necessity for either the wife, husband, or children to have a blood Wassermann made is also explained. These cases are care-

No. 4

SOCIAL SERVICE
IN
BARNES HOSPITAL
ST. LOUIS CHILDREN'S HOSPITAL
WASHINGTON UNIVERSITY DISPENSARY

MAINTAINED BY
ST. LOUIS ASSOCIATION FOR SOCIAL WORK

507 S. EUCLID AVE.
ST. LOUIS, MO.
FOREST 7400
STATION 80.

Dear Friend:-

Your doctor at the dispensary wants you to report to the Skin Clinic as soon as possible. Your blood test proved to be positive, which means that it is very important for you to have treatment now before other complications might arise.

If you cannot return now, or if you are under the care of a private physician, kindly reply at once.

Yours very truly,

(Miss)

Social Worker.
Skin Clinic.

Fig. 14.—Letter sent when a positive Wassermann test is reported to any of the clinics and the patient fails to return for treatment.

fully followed with the result that a large percentage report to the clinic. Children having a positive Wassermann are treated in the Pediatrics clinic, (Appendix B). A special worker is in charge of the supervision of these cases. Literature on venereal diseases, suitable to the sex and age of the patient, is given. (Appendix G.)

While the interview with the patient is taking place the social history is obtained (Figs. 16 and 17). The social worker by this means gains an insight into the patient's living and working con-

ditions. If circumstances do not permit regular attendance at the clinic she makes the needful adjustments. In some cases it is necessary to treat patients without the customary admission charge of twenty-five cents and the additional charge of ten cents for mercury injections. If, during the interview, there is evidence of a social problem such as needed material relief or unemployment, the patient is referred to the proper social agencies. Patients who are handicapped are referred through the vocational clinic to the placement bureau or, where a certain type of work is desired by the doc-

No. 5

SOCIAL SERVICE
IN
BARNES HOSPITAL
ST. LOUIS CHILDREN'S HOSPITAL
WASHINGTON UNIVERSITY DISPENSARY

MAINTAINED BY
ST. LOUIS ASSOCIATION FOR SOCIAL WORK

507 S. EUCLID AVE.
ST. LOUIS, MO.
FOREST 7600
STATION 86

Dear Friend:-

You were to have two doses of Salvarsan at the Municipal Clinic and then return to our Skin Clinic for treatments on Wednesday and Saturday afternoons. Your doctor here wants to know why you have not returned as he advised. Your disease, you know, is a serious blood disease which may affect any and all parts of your body. If you are under the care of a private physician let us know and we will scratch your name from our list.

We hope you will return or reply at once to

(Miss)

Social Worker,
Skin Clinic.

Fig. 15.—Letter sent when patient who has been sent to the Municipal Clinic for arsphenamine fails to report back to the skin clinic.

tors, to our workshop for occupational therapy, (Appendices H and I). In cases where the problem involves the young girl or boy, contact is made if possible with the Girls' Protective League, or the Big Sister or Big Brother Organizations.

Appointments for arsphenamine injections are made by the social worker who may cancel the charge of two dollars and a half when the occasion demands. All patients who have never been given arsphenamine in this dispensary are referred to the medical clinic

first for an examination. One refer slip is given the patient and another marked "Examination for '606'" is attached to the medical history. The treatment card is marked with an "S" on the appointed date. The "follow-up" card is also marked in the same way. The name of the patient with the clinic number and whether or not the arsphenamine is to be given free is written in the calendar book for that purpose. Form No. 17 (Fig. 8), carefully explained and filled out, is also given. If it is difficult for the patient to leave his work in order to have the physical examination, a special appointment slip is given so that he may be examined the same day shortly before the arsphenamine is given. This saves him an extra trip to the dispensary. If the doctors in the medical clinic advise that the patient be given arsphenamine in the hospital in place of in the clinic, the social worker arranges for hospital care.

The majority of infectious cases are referred to the Municipal Clinic for two doses of arsphenamine with a card from the social worker. They then return to our clinic for routine treatment.

All infectious cases are reported by card to the Board of Health by the clinic secretary, the clinic number only being given. By a system of cooperation between the chief diagnostician of the Board of Health and the social worker, those infectious cases sent to the Municipal Clinic are reported to him directly by name and address. If these patients fail to report immediately, the Board of Health notifies the Police Department and they are brought to the Municipal Clinic by plain clothes men or police women and given treatment.

The clinic secretary keeps a list of all new patients with a positive Wassermann. If these fail to return as directed, letter No. 4 (Fig. 14) is sent. Positive Wassermans from all other clinics are also followed and the patient urged to report to the Skin clinic for treatment. If the infectious patients sent to the Municipal Clinic for arsphenamine do not return within a reasonable time, letter No. 5 (Fig. 15) is sent. Patients who fail to return after starting treatment are sent a postcard (Fig. 10) after a week's absence. If there is no response, letter No. 1 (Fig. 11) is sent. After another week without response, letter No. 2 (Fig. 12) is sent. If the patient has not returned within another week a home visit is made to emphasize the necessity for continued treatment. Letter

SOCIAL SERVICE DEPARTMENT No. A 1335

BARNES HOSPITAL, CHILDREN'S HOSPITAL, WASHINGTON UNIVERSITY DISPENSARY

Full Name BLANK, BESSIE Phone _____ Date 5-1-19Address 3719 Blank Street Rooms 2

Cross Ref. _____

Key No.	Members of Household	Patients	Relation to Number	Age	Sex	Conjugal Condition	Religion	Birthplace	Nationality	Time in U. S.	Time in City	Citizen	Health
1	Albert		Husb	35	M	M	Ill.	Amer.		6 mo.			Luetic
2	Bessie	✓		28	F	M	" Ill.	Amer.					Pregnant
3	Madge			11	F								Good
4	Clark			4	M								"
5	Arthur			2½	M								"

WORK OR SCHOOL RECORD

Key No.	Where Employed School How long out of Work	Date	Trade Process or Grade	Hours per Week	Wage per Week	Employer Foreman Teacher
1	Auto Works	5-1-19	Cutter	55	\$20	Mr. Smith

FINANCIAL STATUS OF FAMILY

Weekly Income	Date	Amt.	Date	Amt.	Weekly Outgo	Date	Amt.	Date	Amt.
Total Weekly Wage					Rent-Board	5-1-19	5.00		
Lodgers Etc.					Insurance		1.15		
Benefits					Groceries		10.00		
Workman Comp.	not paid	\$6.00			Coal		1.00		
Other Sources					Carfare		1.20		
Total Weekly Income					Total Outgo		18.35		
Savings					Debts		50.00		

Fig. 16.—Social Service record (front). Color, yellow.

Key	Date Ref'd	Dr. or Clinic	Worker	Agency	Remarks
2	5-1-19	Skin	E.B.	Social Service Dept.	
2	5-1-19	Obstetrical	A.C.S.	" " "	Co-operating
2	5-1-19			St. L. Provident Assn.	Co-operating

PREVIOUS MEDICAL HISTORY				PRESENT MEDICAL TREATMENT				
Key	Where Treated	Date	Diagnosis	Key	Clinic Ward	DATE JUN. 1939	Diagnosis	O. P. D. No.
2	Obstetrical	5-1-19	Pregnancy (5 mo.)	2	Skin		Lues-Secondaries W.R. 4+	A20139

RELATIVES-AGENCIES-CHURCH-PREVIOUS EMPLOYERS, ETC.				
Key	Date	Connection	Name	Address
2	5-1-19	Parents	John and Mary Simmons	Illinois
1	5-1-19	Brother	James Blank	Texas

Date	Previous Address	Date	Previous Address
4-1-18	3112 Blank		

Social Difficulties

Possibility of infecting children
Children need shoes and clothing

Registered by others *No* Registered by S. S.

Social Diagnosis *Insufficient income due to
enforced idleness caused by accident.*

CLASSIFICATION ACCORDING TO TYPE OF CASE			
Instructive	Social	Supervisory	Diagnosis Only
	5-1-19		
Date	Final Disposition 10-2-19 <i>Closed</i>		
<i>No further adjustments necessary.</i>			

Fig. 17.—Social Service record (back). Color, yellow.

#1	Blank, Bessie	2719 Blank St.,	#2	Blank, Bessie
E.B. Introduction	5-1-19 E.B. interviewed #2 in Clinic. Patient was referred to the Social Worker for instructions and for an appointment for Arphenamine.		E.B.	family is in debt for a grocery bill of fifty dollars(\$50.00). #2 contracted syphilis from #1 who became infected a few weeks ago. #1 received two doses of Arphenamine at the Municipal Clinic. #1 and 2 are very devoted to one another. #1 is greatly distressed that he is the cause of her infection.
Description.	#2 is a very refined, pretty little woman. She cried and seemed broken hearted over the diagnosis given her by the doctor.		Action	The Bernard Hospital, which co-operates with the Skin Clinic here, was telephoned to, and arrangements made for the patient to get Arphenamine there the next day. This arrangement was made, as it was not possible to give Arphenamine here for two days, and it was thought advisable not to refer her to the Municipal Clinic.
Doctor's statement	The doctor stated she was in an infectious condition of syphilis and must have Arphenamine immediately. He referred her to the Obstetrical Clinic as she is pregnant and not under the care of a physician.			The need for shoes and clothes was discussed and it was decided, with the patient's consent, that application be made to the St. Louis Provident Association.
First interview	#2 stated she, with her husband and three children, came here from ----- Illinois six months ago. She had lived there all her life. Her people had been in comfortable circumstances and she had been given a high school education. Her husband had worked in the mine in ----- Illinois and they had gotten along very well until last April when he was injured. He was unable to work from April 1918 until January 1919. He has never received compensation, as it is still in abeyance, however he expects to get it in time. At present he is working for the ----- Automobile Works Company and earning twenty dollars a week. They had used all their savings during the period #1 was unable to work. The parents of #2 are living, but unable to help. #1 has a brother in Texas, but never hears from him. Only one child is of school age. She is attending the ----- School. The family is Protestant, but have not joined any church since coming to St. Louis. At present they are living in two furnished rooms. #1 hopes to get a better paying position soon and then they will move to a better neighborhood. The children are in need of clothing and shoes and the		Registration	E.B. telephoned the Social Service Exchange The family is not known there.
			Home Visit.	5-2-19 E.B. reported case to the Provident Association.
				5-5-19 Home visit made by ACS, Social Worker for the Obstetrical Clinic, to instruct patient in the Hygiene of pregnancy. Worker found rooms very neat and clean, and conditions for light housekeeping fairly good.
				5-8-19 Report received from the Provident Association stated that they had made an investigation and had provided the necessary clothes and shoes for the children.

Fig. 18.—Social Service record continuing typical social history.

Fig. 19.—Social Service record continuing typical social history.

#3	Blank, Beale	#4	Blank, Beale
E.B.	<p>5-9-19 E.B. interviewed #2 at clinic. She received the dose of Arphenamine at the Barnes Hospital on 5-2-19 and had no reaction. She will take the other two doses a week apart here with the mercury injections in between. She is anxious to take the treatments regularly and has urged #1 to come out for a Wasserman. He will try and come out on Thursday afternoon and will bring the children for a Wasserman.</p> <p>5-16-19 E.B. interviewed #1 at clinic. His Wasserman report is positive and he was put on regular treatment. He was given a refer slip to the Night Clinic to avoid losing time from his work. The Wasserman report on the children is negative.</p> <p>6-12-19 ACS of the Obstetrical Clinic reports that #2 is most co-operative. She is reporting regularly to that clinic. #1 is reporting regularly to the Night Clinic and #2 regularly to the Skin Clinic in the afternoon.</p> <p>7-20-19 E.B. interviewed #2 in Clinic. #1 has been paid his compensation of \$600.00. He has paid the Provident Association \$25.00 for the shoes and clothes supplied by them. They have moved in to a better neighborhood recently and have a four room flat. They are paying on furniture for this. #1 is feeling so much better since he started the treatments here, that he has been given a better position with his company and is now earning \$30.00 a week. #2 wants to be confined in Barnes Hospital and will pay for her care. The Social Worker in the Obstetrical Clinic will make arrangements for this.</p>	E.B.	<p>8-18-19 #2 was delivered at Barnes Hospital. A boy.</p> <p>9-24-19 Worker for Obstetrical Clinic reports both mother and baby are doing well. The Wasserman on the baby was negative.</p> <p>10-2-19 E.B. interviewed #2 with baby at clinic. #2 has been taking the baby to the Well Baby Clinic, on the advice of the Obstetrical Worker. The baby had another Wasserman taken in the Pediatrics Clinic and the report was again negative. The mother is deeply grateful for the interest taken in her case. She feels that the care given her is responsible for her healthy baby. She intends to continue her treatments in the Skin Clinic. #1 continues to report regularly to the Night Clinic.</p> <p>No further adjustment necessary. #1 and 2 to be followed, by card by the Clinic Secretary. Case closed.</p>

Fig. 20.—Social Service record continuing typical social history.

Fig. 21.—Social Service record continuing typical social history.

No. 3 (Fig. 13) is sent to those patients who fail to report for their arsphenamine injection.

SKIN CLINIC STATISTICS FOR NOVEMBER, 1919

Total number of syphilitic patients.....;.....	818	
(some being on rest periods)		
Discontinued treatment	39	- 5%
Accounted for as follows:		
Not located	22	-56%
Under private care	5	
Left the city	8	
Died	1	
Advised to discontinue	1	
Sent to Koch (T. B. C.) Hospital	1	
Sent to City Infirmary	1	
Total number located	17	-44%
Number of new cases of syphilis	56	
Number of infectious cases	11	
Number sent to Municipal Clinic	8	
Total arsphenamine injections	96	
Total mercury injections	965	
Average attendance at night clinic	90	
Average free arsphenamines per week	3	
Average free Wassermanns per month.....	200	
Out of a total attendance of 1318, 776 were repeaters on the 8 treatment days in the month, giving as an average per treatment day..	97	
Social service work.		
Postcards and letters sent	295	
(some patients received 1 card and 2 letters)		
Replies received from the above	89	-30%
(not necessarily indicating that they all returned to the clinic)		
Home visits made	67	
Number located	35	-52%
Successful visits (returning when located)	9	

Appendix "A"

FINANCIAL STANDARDS OF ADMISSION TO THE WASHINGTON UNIVERSITY DISPENSARY

A basic financial standard was established in 1916 by a committee consisting of Dr. G. Canby Robinson, Dr. Borden S. Veeder, and Miss Julia Stimson, head social service worker. In their very complete study of this question they reached the conclusion that "the weekly wage rate sufficient for the bare cost of living for a normal family throughout the year without providing for health or savings" was "\$80 a month or \$18.50 a week." From this basic figure, tables were constructed so that all family conditions were taken into consideration,—number of adults, number of children at varying wages, number of wage earners, single men, single women, etc. For a complete discussion with tables, etc., the reader is referred to the original article.*

The clinic administrator makes a thorough inquiry into the financial status of the patient upon admission, using these standards as a basis. However, as

*Veeder, B. S.: Jour. Am. Med. Assn., (July 8) 1916, lxxvii, 85.



City of St. Louis, Missouri.

DEPARTMENT OF PUBLIC WELFARE
DIVISION OF HEALTH

"606"

**"SYPHILIS", better known as "POX", has de-
stroyed, crippled and wrecked more lives than**

THE GREAT WAR NOW GOING ON.

Any sore on your privates may wreck your future.

**No matter how trivial it may seem to you, don't
undertake to treat yourself or accept the advice of
friends or advertising doctors. If you cannot employ
a reputable physician, the Health Department offers
you, the most scientific advice and treatment "606",
in its purest form, administered by experts.**

"FREE"

Call at Room 35 Municipal Courts Building, 14th and Market Sts.

Office hours: 8.30 A. M. to 5 P. M.

All interviews private and confidential.

they were established in 1916, full allowance is made for the increase in the cost of living since that time.

Appendix "B"

All cases of syphilis in children under the age of 14 are treated by the Pediatrics clinic.

Every other case of syphilis, including neurologic, visceral, ophthalmologic, otologic, etc., is sent to the dermatologic clinic for treatment. In other words, all syphilis except that in children, is treated by the department of Dermatology.

Appendix "C"

CLINIC SECRETARIES—VOLUNTEERS

Volunteers have always been associated with the activities of the Social Service Department. They have served in various capacities, some assisting the doctor, some the social worker, and others helping in the clerical work of both. With adequate educational background and interest in the subject, college graduates are assisting the psychologist in taking histories in the Neuropsychiatric clinic. Volunteers are also of help in recording the medical findings in the Eye clinic. A number of graduate dietitians who come from various universities for hospital experience under the direction of the dietitian of Barnes Hospital volunteer their services in the dispensary too. They assist in giving instructions, both in the clinic and the home, to patients needing special diets.

The volunteers who assist in home visiting are under the supervision of the social worker. They are of special value in the simple "follow-up" cases. "Social cases"—those requiring skill in social diagnosis and treatment—are entrusted only to those unpaid volunteers who have had training in social work or who are students in training at the Missouri School of Social Work doing field work under the direction of the Social Service.

The clinic secretaries are the volunteers who have charge of the clerical "follow-up" work in the clinic. They serve in many ways as secretaries to both doctor and social worker and frequently as clinic executives, taking the responsibility of the clinic routine.

The social service department also has a motor corps of volunteers who bring certain patients to and from the clinic or take social workers on their round of visits.

The average number of volunteers serving at any one time is about forty; the number of persons who serve during a year, about one hundred and fifty.

Appendix "D"

CLASSIFICATION OF SYPHILIS ACCORDING TO MARTIN F. ENGMAN, M.D.

- I.—Syphilis Primary—from the very first appearance of the chancre to the appearance in the blood of a positive Wassermann reaction.
- II.—Syphilis Early—from the first appearance of a positive Wassermann reaction or a generalized eruption to the entire disappearance of generalized spirochetal lesions or highly infectious lesions.

- III.—Syphilis Late—gummatous lesions, no matter where located, in other words, local syphilis.
- IV.—Syphilis Latent—a positive Wassermann reaction with no demonstrable clinical lesions.
- V.—Neurosyphilis—including tabes, paresis, and all other manifestations in the central nervous system.

Appendix "E"

EXPENSE OF CLINIC TREATMENT TO THE PATIENT

For every visit to the the dispensary an admission fee of twenty-five cents is charged.

For every mercury injection, a fee of 10 cents is charged.

For every arsphenamine injection, the charge is \$2.50.

Wassermann tests are free.

All prescriptions are filled at a standard rate of twenty-five cents, no matter what the contents may be.

Therefore, the minimum expense to the patient for one "course" of treatment is \$15.50.

To this might be added carfare at fifteen cents per visit, adding \$3.60 to the above, or a total of \$19.10 per "course."

Appendix "F"

BOARD OF HEALTH SIGNS

The St. Louis Health Department, in order to bring to the attention of those most likely to be in need of treatment the fact that arsphenamine can be obtained without cost, has posted in many toilet and dressing rooms of factories, business houses, public comfort stations, etc., the metal sign shown in Fig. 22. This sign was gotten up by Dr. M. F. Engman for the health department, taking as a model the advertising used by "quacks."

Appendix "G"

VENEREAL DISEASE LITERATURE DISTRIBUTED AMONG PATIENTS

- I.—Our Form No. 16 (see Fig. 9), which is a list of instructions to syphilitics.
- II.—United States Public Health Service V. D. Pamphlet No. 6, issued by the Treasury Department and entitled "Manpower."
- III.—United States Public Health Service V. D. Pamphlet No. 1, as revised February, 1919, and entitled "Keeping Fit."
- IV.—New Jersey State Board of Health Folder V. D. No. 33, entitled "To Girls in Industry About the Enemy at Home."
- V.—New Jersey State Board of Health Folder V. D. No. 32, entitled "The Parents' Part."

Appendix "H"

THE VOCATIONAL CLINIC AND RED CROSS PLACEMENT BUREAU

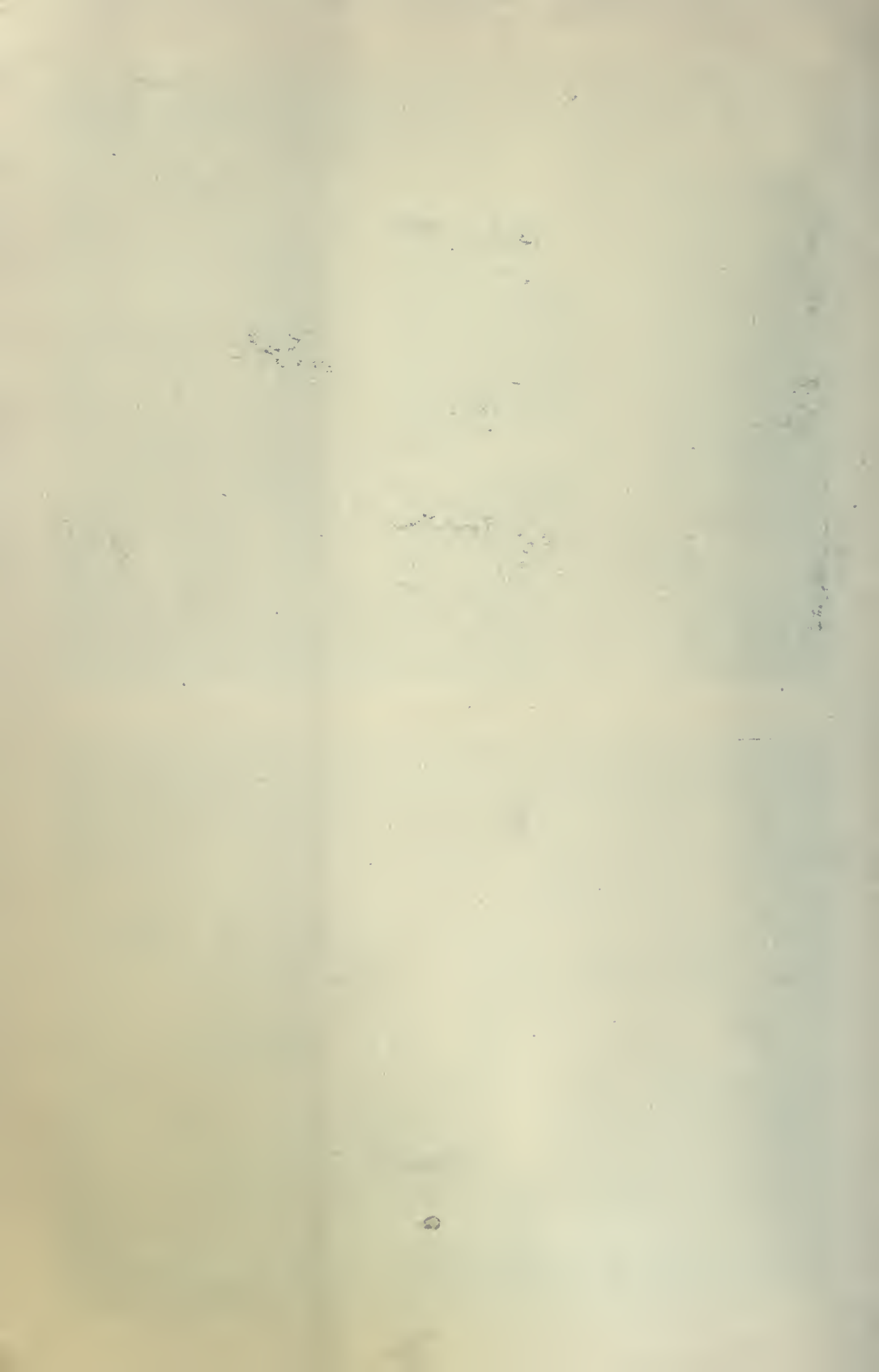
The Vocational Clinic is held each Saturday morning. To it are referred, by doctors and social workers in any of the clinics of the dispensary, patients who



Fig. 23.—Treatment room for women.



Fig. 24.—Arsphenamine treatment room.



are handicapped and who seem to be misfits in the industrial world. A representative of the Red Cross Placement Bureau is present, who confers with the doctor, the social worker, and the patient. The point of view and the knowledge which each can give is important in deciding what sort of occupation is most advisable. The Bureau has attempted the placement of nerve syphilitics with a good deal of success.

An inmate of the city infirmary, who had suffered from locomotor ataxia and improved under spinal treatment, was referred to the clinic recently. He had been a mechanic. He is now a shoe repairer for a company which is well pleased with his work. The case is experimental and the patient is still under the observation of the clinic.

Syphilitic patients, not handicapped except in the fact that worry has reduced their powers of concentration, have also been placed by the bureau. These sometimes require, before placement, a trial period of occupational therapy, in the Junior League Workshop.

Appendix "I"

THE JUNIOR LEAGUE WORKSHOP

The Junior League Workshop was opened March 1, 1917, for the purpose of giving employment to handicapped patients from the Washington University Dispensary and Barnes Hospital. It is under the direction of a committee composed of three members of the medical staff of the dispensary, three members of the social service, and three members of the Junior League. The Junior League of St. Louis is responsible for its maintenance.

It is the aim of the workshop to give needy men and women the benefit of regulated work as a therapeutic measure and also to make them at least partially supporting. The shop, in connection with the treatment received at the dispensary, has been of great aid to many patients because it has provided them with proper employment under favorable conditions during the period of convalescence, when it would have been impossible for them to undertake work except under the special conditions which the workshop provides. It has also been therapeutic in proving to patients who have lost confidence, that they can do something successfully.

Patients are recommended for the workshop by the doctors. They are then interviewed by the social service, whose worker keeps in close communication with the man or woman while in the shop. Those most benefited have been those suffering from cardiac, neurasthenic, or orthopedic conditions.

Weaving, toy making, and cement work is done.

STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. IX

A COMPARATIVE STUDY OF COMPLEMENT FIXATION IN SYPHILIS WITH ANTIHUMAN, ANTICHICKEN, AND ANTISHEEP HEMOLYTIC SYSTEMS*

BY JOHN A. KOLMER, M.D., TOITSU MATSUNAMI, M.D., AND ANNA
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(Received for publication, November 22, 1919)

THE primary purposes of this investigation were a comparative study of several hemolytic systems in the conduct of complement-fixation tests in syphilis to determine their relative delicacy, and secondly, a further study of the influence of natural antisheep hemolysin in human sera upon complement-fixation tests conducted with an antisheep homolytic system; as previously stated¹ the subject of a hemolytic system for a standardized complement-fixation test is one of primary importance requiring a large amount of careful unbiased study.

A great deal has been written upon the comparative results of complement-fixation tests conducted with an antisheep system after the method of Wassermann and an antihuman system after the method of Noguchi. Unfortunately much of this work was not strictly comparative or adapted for critical analysis inasmuch as the technic of the two methods usually varied in one or more essential details, among which may be mentioned whether the sera were heated or unheated, and whether the primary incubation was conducted in a thermostat or in a water bath; these factors have an important bearing upon the results and in strictly comparative tests the technic should be identical in all details. Furthermore, much of the work reported in literature was conducted with one kind of antigen in the Wassermann tests and a different antigen in the Noguchi tests, and the tremendous influence exerted

*Aided by funds accruing from the preparation of arsphenamine.
Read in part before the Fourth Annual Meeting of the American Association of Immunologists, New York, May, 1917.

upon the results of any method by the kind of antigen employed is well known; likewise the investigations of Morgenroth and Sachs² have shown that the activity of hemolysins bears a close relationship to the amount of complement in the hemolytic system, and for this reason tests for the determination of the influence of natural antish sheep hemolysin in human sera upon complement-fixation based upon comparative results with antish sheep and antihuman hemolytic systems should be conducted with similar amounts of complement in the hemolytic system.

METHOD OF STUDY

In this investigation a large number of sera were subjected to comparative tests with antish sheep, antiox, antichick en and antihuman hemolytic systems; as previously stated³ human and guinea pig sera contain less antiox than antish sheep hemolysin and are practically free of hemolysins for human and chicken corpuscles. By using these hemolytic systems we have attempted an accurate determination of the influence of natural hemolysins in human and guinea pig sera (complement) and particularly that for sheep cells, upon the results of complement-fixation reactions and have sought to arrive at a decision upon the important question regarding the best hemolytic system for a standardized complement-fixation test. For these purposes a large number of sera have been subjected to strictly comparative tests being used in the same amounts, with the same antigens, and an identical technic throughout.

TECHNIC

All sera were *heated* in a water-bath at 56° C. for thirty minutes and used in fixed amounts of 0.1 c.c. or in descending doses rendering the tests quantitative for the purpose of eliciting variation in the final results with the different hemolytic systems.

Three different antigens were employed, namely, cholesterolized alcoholic extracts of heart muscle, alcoholic extracts of syphilitic liver and acetone-insoluble lipoids of heart muscle. Each extract was carefully titrated and *used in all tests in the same amounts*.

Two hemolytic systems were employed as follows:

1. In complement-fixation tests employing an antihuman and antichick en hemolytic system, the technic of the U. S. Army devised

by Craig and Vedder was employed; Craig dilutes guinea pig serum complement with an equal part of salt solution, whereas Vedder dilutes 1:1½ and we have used the latter. Corpuseles were employed in constant dose of 0.1 c.c. of 5 per cent suspensions and each complement in two units, all titrations of hemolysin, complement, and antigens and the main tests being conducted in exactly the manner described by Craig⁴ and more recently by Vedder.⁵

A large proportion of the tests employing antisheep and antiox hemolytic systems were also conducted with the same technic.

2. Tests with an antisheep and antiox hemolytic systems were also conducted with a regular Wassermann technic, employing half amounts; complement was used in constant dose of 1 c.c. of 1:20 dilution, corpuseles in dose of 1 c.c. of 2½ per cent suspensions and the hemolysin titrated with each complement and corpuscle suspension and used in the main tests and titrations in two units. The primary and secondary incubations were conducted in a water-bath in exactly the same manner as tests employing the antihuman and antichicken systems.

Sera were generally tested in groups of twelve or more in order that the tests with the different hemolytic systems could be conducted at the same time with the same complements and antigens and under identical conditions.

All reactions were read after the tubes had stood for sixteen to twenty-four hours in a refrigerator after the secondary incubation.

RESULTS

These are summarized and presented in the form of tables; Table I gives a summary of the results observed with 100 sera from syphilitic persons receiving treatment in the clinic of Professor Schamberg, tested in amounts of 0.1, 0.01, 0.001, 0.0001 and 0.00001 c.c. with a cholesterolized extract of heart and with anti-sheep, antichicken, and antihuman hemolytic systems, all tests being conducted with the technic of Craig and Vedder. Table II gives the details with 10 of these sera tested with antisheep and antihuman systems, inasmuch as Table I does not give the variations in degree of complement fixation. Table III summarizes the results of tests conducted with an antihuman and antichicken hemolytic system with an additional 48 sera from syphilitic persons undergoing treatment, tested in descending amounts.

TABLE I

SUMMARY OF RESULTS OF COMPARATIVE COMPLEMENT-FIXATION TESTS WITH 100 SYPHILITIC SERA IN VARYING AMOUNTS AND ANTISHEEP, ANTICHICKEN, ANTIHUMAN HEMOLYTIC SYSTEMS*

HEMOLYTIC SYSTEMS	PERCENTAGE OF POSITIVE REACTIONS				
	0.1 c.c. Serum	0.01 c.c. Serum	0.001 c.c. Serum	0.0001 c.c. Serum	0.00001 c.c. Serum
Antisheep	95	70	16	0	0
Antichicken	97	79	25	5	0
Antihuman	97	78	25	6	0

*All sera were heated at 56° C. for thirty minutes; all tests conducted with cholesterolized extract.

TABLE II

COMPARATIVE COMPLEMENT-FIXATION TESTS WITH ANTISHEEP AND ANTIHUMAN HEMOLYTIC SYSTEMS

SERA	ANTISHEEP SYSTEM					ANTIHUMAN SYSTEM				
	0.1 c.c.	0.01 c.c.	0.001 c.c.	0.0001 c.c.	0.00001 c.c.	0.1 c.c.	0.01 c.c.	0.001 c.c.	0.0001 c.c.	0.00001 c.c.
1.	++++	++++	-	-	-	++++	++++	+	-	-
2.	++++	++++	+	-	-	++++	++++	+	±	-
3.	++++	++	+	-	-	++++	++	+	±	-
4.	++++	++	-	-	-	++++	++	±	-	-
5.	++++	++++	+	-	-	++++	+++	+	-	-
6.	++++	++++	+	-	-	++++	++++	+	+	-
7.	++++	+	-	-	-	++++	+	-	-	-
8.	++++	+	+	-	-	++++	++	+	-	-
9.	++++	++	-	-	-	++++	+	-	-	-
10.	++++	++++	-	-	-	++++	++++	-	-	-

TABLE III

SUMMARY OF RESULTS OF COMPARATIVE TESTS WITH 48 SERA IN VARYING AMOUNTS WITH ANTIHUMAN AND ANTICHICKEN HEMOLYTIC SYSTEMS*

HEMOLYTIC SYSTEMS	PERCENTAGE POSITIVE REACTIONS				
	With 0.1 c.c. serum	With 0.05 c.c. serum	With 0.025 c.c. serum	With 0.0125 c.c. serum	With 0.00625 c.c. serum
Antihuman	75	67	50	33	25
Antichicken	74	65	50	33	25

*All sera heated; all tests conducted with a cholesterolized heart extract.

As shown in these tables, and particularly in Table I, the anti-sheep system has not proved quite as sensitive as the antihuman and antichicken hemolytic systems *and especially with sera tested in amounts smaller than 0.1 c.c.* The results observed with the antihuman and antichicken systems were closely parallel; sometimes the antichicken system appeared to yield stronger reactions with smaller

amounts of serum, but the total results as shown in the tables have been nearly the same with both systems, and the differences within the range of experimental error.

In Tables IV, V, and VI are shown summaries of the results of tests conducted with two different methods, that is, the tests with antishoop and antiox systems were conducted with the one-half Wassermann method and those with the antichicken and antihuman systems with the army method.

TABLE IV

SUMMARY OF RESULTS OF COMPARATIVE COMPLEMENT-FIXATION TESTS CONDUCTED WITH 120 SYPHILITIC SERA IN AMOUNTS OF 0.1 C.C. AND DIFFERENT HEMOLYTIC SYSTEMS

HEMOLYTIC SYSTEMS	PERCENTAGE OF POSITIVE REACTIONS		
	Cholesterolized Antigen	Syphilitic Liver Antigen	Acetone-Insoluble Lipoids
Antisheep	92	85	90
Antiox	97	93	94
Antihuman	98	97	97

TABLE V

SUMMARY OF RESULTS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH 76 SYPHILITIC SERA AND VARIOUS HEMOLYTIC SYSTEMS*

HEMOLYTIC SYSTEMS	PERCENTAGE POSITIVE REACTIONS				
	With 0.1 c.c. serum	With 0.05 c.c. serum	With 0.025 c.c. serum	With 0.0125 c.c. serum	With 0.00625 c.c. serum
Antisheep	87	76	57	33	26
Antiox	89	84	66	43	30
Antichicken	86	82	70	56	43
Antihuman	91	87	79	58	45

*All tests were conducted with a cholesterized extract of heart for antigen.

TABLE VI

SUMMARY OF RESULTS OF COMPARATIVE COMPLEMENT-FIXATION TESTS CONDUCTED WITH 130 SERA WITH ANTISHEEP AND ANTIHUMAN HEMOLYTIC SYSTEMS*

ANTIGEN	BOTH POSITIVE	BOTH NEGATIVE	ANTISHEEP POSITIVE ANTIHUMAN NEGATIVE	ANTISHEEP NEGATIVE ANTIHUMAN POSITIVE
Cholesterolized Heart	52 per cent	37 per cent	None	11 per cent
Acetone Insol. Lipoids	44 per cent	46 per cent	None	10 per cent

*All sera heated and used in dose of 0.1 c.c.

As shown in Table IV the antiox system proved superior to the antisheep and the antihuman was superior to both; this table also shows the marked differences in results observed with different antigens, best results being observed with cholesterolized extracts and poorest with alcoholic extracts of syphilitic liver. Table VI also shows the superiority of cholesterolized extracts over acetone insoluble lipoids and the superior delicacy of the antihuman versus the antisheep hemolytic systems.

A few tests were also conducted after the quantitative method of Browning and McKenzie consisting in using the sera in constant amounts of 0.1 c.c. with constant amounts of antigen and increasing amounts of complement. The anticomplementary activity of each serum and the antigen are also measured with one and two units of complement, and subtracted from the number of units of complement fixed by the mixtures of serum and antigen. We have tested a few syphilitic sera with this method employing an antihuman and antisheep system with complement diluted 1:1½; the results with five sera are shown in Table VII and a summary of tests with twenty-four additional sera in Table VIII. Owing to the large amounts of complement required, the method is quite expensive when used on a large scale.

TABLE VII

COMPARATIVE RESULTS IN QUANTITATIVE COMPLEMENT-FIXATION TESTS WITH ANTISHEEP AND ANTHUMAN HEMOLYTIC SYSTEMS

SERA	HEMOLYTIC SYSTEMS	COMPLEMENT-FIXATION SERIES*							SERUM CONTROLS		
		2 Units	3 Units	4 Units	5 Units	6 Units	7 Units	8 Units	1 Unit	2 Units	Units of Complement Fixation
3S	Antisheep	+++	++	+	+	-	-	-	+	-	4
	Antihuman	+++	+++	+	+	-	-	-	+	-	4
P13	Antisheep	++++	++	-	-	-	-	-	+	-	2
	Antihuman	++++	++	-	-	-	-	-	+	-	2
P26	Antisheep	++++	++++	++++	+++	++	++	-	+	-	6
	Antihuman	++++	++++	++++	++++	++	+	-	+	-	6
P40	Antisheep	++++	++++	++++	++	+	-	-	-	-	6
	Antihuman	++++	++++	++++	+++	++	+	-	-	-	7
P41	Antisheep	++	+	-	-	-	-	-	-	-	3
	Antihuman	++	++	+	-	-	-	-	-	-	4

*Conducted with a cholesterolized extract which did not of itself absorb a unit of complement.

TABLE VIII

SUMMARY OF RESULTS OF QUANTITATIVE COMPLEMENT-FIXATION TESTS WITH ANTISHEEP AND ANTIHUMAN HEMOLYTIC SYSTEMS

SERA	UNITS OF COMPLEMENT-FIXATION		SERA	UNITS OF COMPLEMENT-FIXATION	
	Antisheep System	Antihuman System		Antisheep System	Antihuman System
1	4	4	13	5	5
2	2	2	14	2	3
3	2	2	15	4	4
4	5	4	16	6	6
5	3	4	17	8	8
6	6	6	18	3	4
7	5	6	19	2	2
8	4	4	20	3	3
9	2	3	21	4	5
10	4	4	22	2	2
11	4	4	23	6	7
12	2	2	24	4	4

As shown in these tables the results were quite similar, the slight differences, however, being in favor of the antihuman system.

CONCLUSION

1. *With the technic employed* comparative complement-fixation reactions with 503 sera from syphilitic persons under treatment have shown that tests conducted with antihuman and antichickens hemolytic systems were somewhat superior in sensitiveness to those conducted with antisheep and antiox systems.

2. From 2 to 10 per cent more sera from syphilitic persons react positively in an antihuman system than in an antisheep system.

3. An antiox hemolytic system was more sensitive than an antisheep system yielding from 2 to 5 per cent more positive reactions with the sera of syphilitic persons.

4. Antihuman and antichickens hemolytic systems are of about equal sensitiveness in complement-fixation tests with heated human sera.

5. The differences in delicacy of reactions conducted with antisheep, antihuman, and antichickens hemolytic systems were more apparent in tests conducted with 0.01 to 0.001 c.c. of each serum than in tests conducted with 0.1 c.c. serum.

6. Natural hemolysins in human and guinea pig sera and particularly antisheep hemolysins, reduced the delicacy of complement-fixation tests conducted with an antisheep hemolytic system after

the method described and particularly if the results were read after the tubes have stood for sixteen hours or longer in a refrigerator; antihuman and antichickens hemolytic systems were more sensitive and served to detect smaller amounts of syphilis antibody in human sera.

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THE WASSERMANN CONTROL IN THE TREATMENT OF SYPHILIS*

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I BELIEVE no one cares to dispute the statement that of all the characteristics of syphilis none is more responsible for the confusions, difficulties, and even failures in its treatment than that it is so void of recognizable manifestations throughout the greater part of its course. The one stumbling block in the treatment of syphilis is that eternal question, "When is it cured?"

May I recall an interesting fact to your attention? Of all the lesions produced by syphilis there may be said to be but two classes; those in which the pathologic process readily resolves as a result of energetic treatment and those the pathology of which is such that any amount of energetic treatment fails to result in a return to the normal. Let me illustrate. A chancre, skin gumma, and interstitial keratitis, all resolve more or less rapidly as the result of treatment. Such resolution invariably occurs long before the disease itself is eradicated. On the other hand, aortic aneurysm, bone eburnation, and tabes dorsalis, once having occurred, remain in spite of any amount of treatment—even sufficient treatment to cure the causative syphilis itself. Because of this interesting paradox, a lesion as such can never be taken as an index to the cure of syphilis.

There remain but two factors as a basis upon which the cure of syphilis can be decided. Good sound judgment as to the amount of treatment necessary to cure a given case of syphilis is, should be, and always will remain a great, if not the greatest, single factor as a guide in the treatment of syphilis. Such judgment to be good must be predicated upon certain general observations that have acquired universal acceptance.

The time was when syphilis was treated only until obvious lesions were healed. Experience has proved the total inefficiency of such

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treatment. In like manner the theory that excision of the chancre aborted the disease has been exploded. More recently still we have learned from repeated observations that Erlich was without foundation in his hope that by a single injection of his salvarsan syphilis would be cured. One needs to review but a small proportion of the mass of present day literature on the treatment of syphilis to be convinced that mercury, not by the month but by the year, and arsphenamine, not by the dose but by the half dozens of doses, must be given before any hope of a cure of syphilis can be held.

So I say there are certain general observations that must form the basis of judgment regarding the cure of a given case of syphilis. A very strict adherence to these fundamental observations, however, can not render even the best of judgment infallible. This leads us to a consideration of the second great factor forming a basis upon which the cure of syphilis can be decided.

Wassermann in 1906 called the attention of the world to the fact that an aqueous solution of ingredients extracted from a known syphilitic liver would react with the blood serum of a known syphilitic to bind complement. The original interpretation put upon this finding was that within that antigen made by a watery extract from a syphilitic liver there were fundamental organic elements of the spirochete if not they themselves. In other words, that such complement fixation was a specific reaction between ingredients of the spirochete, specific antibodies in the blood serum of the syphilitic and complement.

In the course of a few years, repeated incidents occurred which threw strong suspicion upon the specificity of the original Wassermann test. It remained for Noguchi in 1909 to draw attention to a most peculiar phenomenon. He demonstrated clearly that an acetone-insoluble alcoholic extract of the muscular tissue of the heart of an ox (as well as of various other nonsyphilitic tissues) would answer the purposes of an antigen as well as, if not better than, Wassermann's original antigen made from a known syphilitic liver. This finding proved conclusively the nonspecificity of the complement-fixation test.

The greatest cause of error in the interpretation of our present day luetic complement-fixation tests is a lack of appreciation of the fact that such tests do not detect an element in the blood stream which is directly the product of the spirochete themselves. They

merely detect some element in the blood stream which very commonly occurs in syphilitics and occurs but seldom in those not syphilitic.

It seems very probable that that something detected by the complement-fixation test is a by-product of an active combat between the invading spirochete and the defensive elements of the host. Such a theory at least is the most workable. It readily explains the Wassermann negative period of from one to three weeks following the appearance of the chancre, because during that period it seems very probable that the defensive system of the host has not yet been mobilized and consequently that reaction between spirochete and the defensive system has not begun. In fact is it not true of most infections that for a short period the bodily defense is not mobilized sufficiently to retard appreciably the progress of the disease?

In accord with such a theory, one would certainly expect the occurrence of a positive Wassermann as soon as that tissue defense has been developed. This is precisely the case. That period from the fourth or fifth week of the chancre until the sixth or eighth month of the disease—the so-called secondary stage—is distinctive in that it presents a positive Wassermann in practically 100 per cent of cases.

As the disease progresses beyond the secondary stage, or stage of rash, it is very conceivable that in a certain number of instances the tissue defenses might be sufficiently great that the spirochetes, thought not actually eradicated, would be overcome to a degree where they for the time being offered no combat. Such an interpretation would readily explain the negative Wassermans found in people known to have had untreated syphilis. Carrying the same illustration still further, a recurrence of a positive complement-fixation reaction would be expected at any time later in the patient's life when, through other conditions depleting his bodily resistance, the spirochetes had regained a degree of virulence and again offered combat.

In those few instances of rapidly fatal malignant syphilis a negative Wassermann would be expected as evidence of a lack of bodily resistance sufficient to offer combat to the disease. This also is precisely the case.

In like manner one would reasonably expect that a syphilitic

extremely ill from some other physical infirmity would be so depleted that bodily resistance against the syphilis would be unthinkable. As a matter of fact the complement-fixation test frequently does become negative during severe illnesses and before death.

The theory that the complement-fixation test recognizes a by-product of the reaction of the invading organisms against the defensive system of the host will be found equally applicable to an interpretation of the Wassermann in syphilitics under treatment. The Wassermann of a syphilitic under treatment remains positive just so long as the infecting organisms remain sufficiently active and virulent to offer combat to the host. Just so soon as those organisms are rendered avirulent by treatment combat no longer exists and the Wassermann becomes negative.

It is a common clinical observation that syphilis may be suppressed by treatment to the point of a negative Wassermann and yet in the course of time the Wassermann may return strongly positive. It seems altogether plausible that so long as the Wassermann remains negative, the spirochetes, though not eradicated, are rendered avirulent, whereas a return of a positive Wassermann indicates merely that the organisms have regained their virulence.

In those instances in which a positive Wassermann has, by prolonged treatment, been rendered negative and remained so for several years, it seems entirely plausible that such a case may be considered clinically cured, a negative spinal fluid permitting.

So, in reviewing the instances in which a negative Wassermann is found in the presence of syphilis, we find that it is really to be expected in very early syphilis, in malignant syphilis, and in syphilitics extremely ill or moribund; in untreated syphilitics, whose individual resistance has been sufficient to suppress their disease, and in those syphilitics who have had sufficient treatment to suppress their infection either temporarily or permanently.

"A negative Wassermann means nothing" is an expression very frequently heard. Like most idioms it is born of an excellent idea but very often misleading. As a matter of fact a negative Wassermann properly done and properly interpreted, does mean a great deal, both in the diagnosis of syphilis and as a control in its treatment.

In the consideration of a negative Wassermann it may be truly said that it means nothing to him who fails to consider the history and physical findings of his patient. A positive Wassermann would mean but little more.

As a matter of fact, however, a negative Wassermann in one giving neither history nor evidences of syphilis practically means that that individual has never had syphilis. A negative Wassermann in one complaining only of a generalized rash means almost to a certainty that that rash is not a secondary rash. A negative Wassermann in one giving a definite history of an untreated syphilis some years old probably means that that individual has, through his own physical resistance, at least temporarily suppressed his infection. A negative Wassermann in an individual who has been under intensive treatment means nothing more than that such treatment has temporarily at least suppressed his or her syphilis. Repeated negative Wassermanns over a period of several years mean that the disease has probably been permanently suppressed or clinically cured.

In the consideration of a negative Wassermann in those individuals whose syphilis is years old and remains inactive, as well as those individuals who are under active treatment, one thing must always be borne in mind. Craig has demonstrated beyond question that in individuals whose syphilis is apparently latent the Wassermann frequently varies from month to month. One month it may be negative, two-positive the second month, four-positive the third month, while by the sixth month it may again become negative. Because of this it is necessary that a Wassermann be found negative repeatedly before it is permissible to expect that syphilis in such a case is even temporarily suppressed. Even then before a final conclusion as to its cure is reached, the spinal fluid must be found Wassermann negative because repeated clinical observations have demonstrated clearly that the spinal fluid Wassermann frequently remains positive for some time after the blood has become negative.

So much for the significance attached to a negative Wassermann. The interpretation of a positive Wassermann is much less difficult. It has been established beyond question that the Wassermann test is found positive quite consistently in yaws. The various explanations of this are all open to refutation. Because of the close similarity of yaws clinically, pathologically, serologically, and thera-

peutically there seem at least good grounds for the assumption, that yaws is a disease at least very closely allied to syphilis, if not actually it in a distorted form. If such is ultimately shown to be the case, our confidence in the Wassermann will be materially increased.

Time and again suspicion has been thrown upon the Wassermann by instances in which a positive reaction was found in other diseases clinically recognizable as such, e. g., tuberculosis, cancer, leprosy, and even in acidosis. That tuberculosis, as such, or cancer, as such, can produce a positive Wassermann is as yet far from proved. This much is certain: a positive Wassermann is the exception rather than the rule in such diseases. With this as the case it may yet be clearly shown that those tuberculous and cancerous patients have a positive Wassermann because they also have syphilis.

Yaws in this locality is a medical curiosity, so only on the rarest occasions could it be confused with syphilis. Though the possibility of cancer, tuberculosis, and leprosy giving a falsely positive Wassermann can not be denied, it seems so improbable that the better part of wisdom appears to indicate that that patient be considered syphilitic.

Throughout this paper reference has not yet been made to what is probably the greatest single factor that has tended to discredit the Wassermann in the eyes of the clinician. I am referring to errors in the Wassermann, not inherent in its system, but the result of improper technic. We have frequent evidence that such a danger exists. Failing to appreciate that occasionally an incompetent is allowed to do Wassermans and that even the most skilled technician is, with all of us, not infallible, one is constantly in danger of at times mistaking a diagnosis.

The Wassermann tests for the Marquette Dispensary during the past year have averaged about fifty a month. Of these, about one-third have been positive and two-thirds negative. No month has varied materially from this proportion. During the absence of our technician for a month, the Wassermans taken during that month (about the usual number of fifty) were done elsewhere, and of those, only six were returned positive, and subsequent Wassermans were at variance both with the negatives and with the positives.

Such experiences should lead one to no other conclusion than that the technician was either incompetent or had resorted to the time-honored sink test. As a matter of fact, however, when Wassermanns are done by a competent technician, it is actually surprising to note the regularity with which the test corresponds with the history and findings of the case. Too frequently, however, there is an apparent discrepancy between the report and what was expected. In such instances the test should be repeated once or twice before any credence is placed upon it. This is especially true of those Wassermanns reported neither clearly negative nor positive. A one-plus or even a two-plus Wassermann when repeated is not infrequently found to be clearly negative, proving the falsity of the first test. Conversely, a two-plus or even a one-plus Wassermann, found so on repeated tests, is very strong evidence in favor of syphilis.

In illustration of this point: L. S. presented herself in 1917 complaining of a swelling of the nose with pus and blood appearing in handkerchief. She gave absolutely no history of anything that might warrant a suspicion of syphilis. In fact she was married and had a perfectly healthy husband and four healthy children. The Wassermann was found one-plus three times with a total of five antigens. Arsphenamine and mercury cleared the nasal condition completely and within a year the blood was found repeatedly negative. Several months ago she gave birth to a normal Wassermann-negative child. Our diagnosis of syphilis, made upon these persistent one-plus Wassermanns, was verified by her recent admission that she had had a chancre and a rash and has transmitted her infection to another man—none of which did she admit at first.

So much for a consideration of the interpretation of a Wassermann.

As a basis for this paper I have reviewed carefully the records of some two hundred and fifty cases of syphilis, the treatment of which was controlled by about one thousand Wassermanns and consisted of over two thousand injections of arsphenamine with a proportionate amount of mercury. I do not purpose to burden you with a mass of statistics. The time during which these cases have been observed will not permit any conclusion about the final cure of syphilis. The material, however, does offer ample opportunity for some observations regarding the value of the Wassermann as a

control in the treatment of syphilis, as well as the way in which the various types of syphilis react to treatment.

It is not within the province of this paper to deal with the controversy recently precipitated by Warthin regarding the pathologic aspect of the cure of syphilis. Further corroborative pathologic research may easily prove Warthin's contention that syphilis is never cured pathologically but, unless all present hopes and beliefs are blasted, syphilis will continue to be considered a disease curable clinically in a fairly large proportion of cases.

Much has been written about the relative ease with which primary syphilis may be cured. There certainly can be no doubt that the treatment of syphilis before and after the appearance of the rash are two entirely different stories. It seems timely, however, to draw attention to two factors that bear heavily upon this prevalent opinion of the curability of primary syphilis.

In the first place, the fact that primary syphilis is relatively easy to cure does not in any sense mean that a few injections of arsphenamine with a few months of mercury is sufficient. Six injections of arsphenamine with a course of four months of mercury will usually result in a negative Wassermann, but not always and in those cases in which the Wassermann is rendered negative by that treatment the disease is by no means invariably cured.

The second factor that must be considered in the treatment of primary syphilis is whether or not the Wassermann has yet become positive. Much evidence is accumulating to support the opinion that the development of a positive Wassermann in a primary syphilitic marks the beginning of an entirely different stage in the disease so far as treatment is concerned.

Of twenty cases of primary syphilis treated, five had not yet developed a positive Wassermann. Observation of these cases seems to justify the belief that a course of six injections of arsphenamine with four months of mercury might be considered fairly adequate treatment. Until experience has proved such, however, it seems the better part of wisdom to continue mercury for a longer period. That one injection of arsphenamine is not ample is clearly shown by a Wassermann negative primary syphilitic who went his way after one injection of arsphenamine only to return in nine months with a typical positive Wassermann secondary syphilis. In another instance the Wassermann became positive in spite of the first injec-

tion of arsphenamine, returning negative after the course was completed.

Of the fifteen cases of primary syphilis with a positive Wassermann, eleven were found negative after the first course of six injections of arsphenamine with four months of mercury. That this does not signify a cure is evidenced by one case developing a virulent cerebrospinal syphilis three months after the course was completed. In two of the remaining four instances this preliminary course did not alter the positive Wassermann, but in one of these the chancre was of two and one-half months' duration and in the other several macules about the chest might have constituted an atypical secondary rash. The remaining two cases, one with one and the other with two injections of arsphenamine, were found actively syphilitic a year later, showing the total inadequacy of one or two injections of arsphenamine even in primary syphilis.

In reviewing these cases of primary syphilis it seems that the ideal time to cure syphilis is in the primary stage before the development of a positive Wassermann. The prognosis in primary syphilis after the advent of the positive Wassermann seems nearly as good if a considerably larger amount of treatment is given.

In reviewing some sixty-five cases of secondary syphilis and some eighty-five cases of tertiary syphilis (excluding nervous syphilis) it was surprising to note that there seems to be but little difference in their reaction to treatment. It seems that as a whole secondary syphilis reacts slightly better to treatment than long-standing syphilis but only slightly. In both instances it has been found that the first course of six injections of arsphenamine and four months of mercury renders the Wassermann negative in about one-third of cases and reduces it to a one- or two-plus, in another third. Of those rendered negative, about half return full positive after two months of rest, proving positively that they have not been cured. Even this much success following so little treatment, however, can not fail to warrant the expectation of a reasonable amount of success if treatment is persisted in systematically for several years.

In this series of cases it has been striking to notice the apparent difference in resistance to syphilis exhibited by the two sexes. I recall four instances in which, through the advent of an active syphilis in the child, the parents were examined. In each of these four instances the father was Wassermann positive and displayed un-

mistakable evidences of nervous syphilis. In two instances the mother was perfectly healthy, but had a positive Wassermann. In the two other instances the mother was equally healthy and had a negative Wassermann. In reviewing this series of secondary and tertiary syphilitics it was found that after the first course of arsphenamine and mercury noticeably more women than men became negative, and after becoming negative, showed less tendency to return positive after a rest.

There is an even more striking difference in the reaction to treatment of one individual from that of another. In illustration of this, ten cases have been selected, the syphilis of which was in each case of years' duration. In five cases the average amount of treatment was six injections of arsphenamine and twenty weeks of mercury. In these cases the Wassermann remained persistently negative for over a year. In the other five cases the average amount of treatment was just twice that and in none was the Wassermann influenced.

My experience with inherited syphilis treated by both arsphenamine and mercury has been limited to some dozen cases. It has been sufficient, however, to warrant the conclusion that it is worth while attempting to cure them. From these few cases it has seemed that they react to treatment in about the same way as do adults with acquired syphilis of many years' duration.

About twenty cases of nervous syphilis have been treated with both arsphenamine and mercury. Most of these were cases of early tabes. Of the four cases of paresis, two progressed rapidly in spite of intensive treatment with arsphenamine and mercury. The remaining two seemed clinically and serologically the same. In most instances of tabes there was a slight improvement of symptoms. In all instances, the disease was clinically arrested during the time they were under observation (i. e., none over two years). In three instances of tabes the blood has been rendered repeatedly negative and in two of these the spinal fluid has been rendered practically negative.

As evidence of the curability of at least some cases of clinical tabes consider the following case: A man, past middle age with syphilis of years' standing was first seen with stiff pupils, absent knee jerks, a moderate Romberg, a positive blood Wassermann and positive spinal fluid with a cell count of eighty-five and positive

globulin. After ten injections of arsphenamine, the blood became negative. After a total of forty injections of arsphenamine over a period of a year and a half (the patient refused to take mercury) the spinal fluid was obtained without pressure and found to give a negative Wassermann, a cell count of four, and but the slightest trace of globulin. The physical findings, of course, remained the same.

From this entire series of cases the following conclusions seem justifiable.

1. That the Wassermann offers an excellent control in the treatment of syphilis. That only, however, when taken in consideration with the physical findings and with the past history of the patient including the amount of his treatment.

2. That syphilis in the pre-Wassermann primary stage reacts most readily and surely to intensive treatment.

3. That Wassermann positive primary syphilis can not be cured by a few injections of arsphenamine and a few months of mercury, but when treated intensively and over a long period, offers an excellent prognosis.

4. That there seems good grounds for the belief that many cases of secondary and tertiary syphilis, even of years' duration, when treated intensively both with arsenic and mercury for one, two or three years can be rendered Wassermann negative and apparently cured.

5. That there are promises of some hope of rendering inherited syphilitics permanently Wassermann negative by prolonged treatment with arsenic and mercury.

6. That in at least some cases of early tabes it is possible to render both the blood and spinal fluid negative to the various clinical tests.

CONCERNING THE WASSERMANN REACTION AS THE THERAPEUTIC INDEX FOR SYPHILIS

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IN 1906, Wassermann, Neisser and Bruck¹ published the result of their labors in respect to a biologic test for syphilis. The reaction was regarded as solely diagnostic in character, and was to be so utilized only if the process effected a "positive" result.

In 1909 F. Plaut² recording research regarding this blood test in nervous and mental diseases, made note that antisyphilitic treatment frequently changed a positive to a negative phase. Succeeding years developed the dictum that herein lies the index for syphilitic treatment. At first this had to do with blood serum reactions and then as frequency of spinal punctures increased, the idea of therapy based on the veering of positive to negative result of the spinal fluid, became the vogue. I am not entirely certain as to the source of this postulate. Several years ago I was told that as early as 1911 numbers of American physicians were receiving instructions from J. Citron of Berlin and that this young scientist was at that time teaching the need of attaining the change of positive to negative phase in treatment. Referring to Citron's book on Immunity (1912), following a maze of warnings as to when and where one may rely upon the Wassermann reaction relative to diagnosis, with the use, respectively, of luetic and normal antigen extracts, in association with syphilitic data and in their absence, one finds this single statement "Not before an absolute negative reaction has been attained should specific therapy cease."³

In the same year that witnessed Citron's view published and thereafter, American authors expressed themselves in like vein. Chas. E. Simon⁴ (1912), says "As regards the relation of the Wassermann reaction to the treatment of syphilis with salvarsan and with mercury, the majority of syphilographers are in accord in demanding that the treatment be continued until a permanent negative Wassermann is obtained and maintained. This standpoint is in accord

*The difficulty of effecting a negative reaction in cases of asymptomatic lues, whose only evidence of a still existing old infection is a positive Wassermann reaction even by combined salvarsan and mercury treatment, he makes mention of.

with the view that the Wassermann reaction is a reaction of infection and not of immunity and that the existence of the infection may be inferred so long as the reaction is demonstrated.”*

Thomas and Ivy⁵ (1915), say “As a guide or measure of the effect of treatment, the Wassermann reaction plays almost as important a role as it does in diagnosis.” However, in the same chapter they state that although symptoms usually disappear before the Wassermann becomes negative, occasionally the opposite holds true; that a positive reaction may persist for some time after all symptoms have disappeared indicating that further treatment is necessary and finally that after being rendered negative by treatment, both positive reaction and clinical symptoms may reappear. In so far as the Wassermann reaction shall be the therapeutic indicator, certainly such conditions must leave the practitioner ever in doubt when he shall cease to make spinal punctures for his information. So much for the didactic word of textbooks. A multitude of clinical essays directly or by inference reflect like therapeutic dicta. Of these, one may particularly refer to the authoritative monograph of Head and Fearnside⁶ (1914). Herein 117 cases of syphilis involving the nervous system are searchingly studied. A careful reading of this essay reveals, as always, this incongruous result, namely: on the one hand, tabulation of a striving to change a spinal fluid or serum positive to a negative through treatment, and on the other, the fact that clinical results and laboratory findings by no means regularly accord. In respect to this statement, I have particularly in mind tertiary syphilis involving the nervous system. During active, second stage lues results of treatment and those of a blood or spinal Wassermann reaction are no doubt more often in agreement, although even here as we know, a treatment acquired negative does not always remain so. Also very pertinent to the question of clinical result versus acquired negative Wassermann is the recent statement and proof of Wile and Hasley⁷ that owing to increasing refinement of laboratory technique patients who a few years ago would have shown after treatment, the very desirable negative reaction, must now needs be given an unqualified positive reading.

In the premises, therefore, although the practitioner shall avail

*A query herein suggested is this. Assuming the need to treat syphilitic patients until a positive becomes a negative Wassermann, what shall be the therapeutic guide in cases which show a negative Wassermann from first to last of the period of observation or which remain persistently positive despite sustained antisyphilitic treatment?

himself of the Wassermann test for diagnostic data, must he not ask himself upon what, beyond a growing tradition based upon a postulate, is born the dictum to treat late neural syphilis until blood and spinal fluid become negative and not for a symptomatic cure? We know that in the so-called quarternary stage of lues (paresis), a positive reaction is practically unchangeable, that in tertiary syphilis the Wassermann reaction may remain positive despite sustained treatment, that the reaction becoming negative may later again show positive, that a seemingly obstinate positive after prolonged treatment may later be replaced by a negative reaction without further treatment, that a negative may so remain or become positive after treatment, and, finally, that an individual with no symptoms may experience dire effects from vigorous antisypilitic treatment instituted upon the sole basis of a positive reading, for instance, a fatal exfoliative dermatitis. The laboratory expert is in the dark, as are we all, as to unknown factors concerned in these varying conditions. However considering them, and necessarily putting to one side the consuming wish for an exact and absolute therapeutic criterion, because it does not yet exist, would it not be more scientific and more just to the syphilitic patient to depend upon clinical aspects of his case in respect to treatment as in time antecedent to a biologic test diagnostically invaluable? This thought is emphasized by the fact that meningovascular syphilis of the cerebrum rarely gives a positive Wassermann, so that under these circumstances, in the presence of symptoms not specifically characteristic, dependence upon laboratory findings may convey false security or distinctly result in a wrong therapeutic lead.*

*Head and Fearnside report two cases of epilepsy due to syphilis, each of which showed a negative spinal fluid and two cells to the cubic millimeter. They also report two cases of syphilitic dementia with negative spinal reaction. The writer recently saw a case of epilepsy of luetic origin which showed a negative blood and spinal fluid Wassermann, 8 cells to the cubic millimeter of spinal fluid and a negative butyric acid test.

Neither can the general conclusions of Head and Fearnside regarding localization of lesion and Wassermann result, fail to be of interest. They say (page 79) "Early in this research we were led to believe that the character of the Wassermann reaction in the cerebrospinal fluid in cases of meningovascular syphilis depended mainly on the site of the lesion. If the signs and the symptoms pointed to an affliction of the spinal cord, its membranes or nerve roots, the reaction was usually positive in the spinal fluid and the strength of this reaction was often as great as that in any other condition of syphilitic origin. But the more completely the manifestations were confined to some affection of the cerebrum or its vessels, the more often was a negative reaction obtained in the cerebrospinal fluid. Even when a positive reaction was present, it was relatively feeble and usually transitory.

Between the cerebrum, on the one hand, and the spinal cord on the other, stands the behavior of the reactions with affections of the cranial nerves produced by meningovascular syphilis. Sometimes the cerebrospinal fluid gives a positive, sometimes a negative reaction according to the extent and situation of the signs and symptoms." And again (page 84), "Thus we have been able to show that in the case of meningovascular syphilis, the key to the Wassermann reaction in the cerebrospinal fluid lies in the presence of inflammatory changes in the meninges of the spinal cord and brain stem. If they are affected, the reaction is positive, while if they have escaped, the cerebrospinal fluid reacts negatively."

To again relegate the Wassermann reaction to its diagnostic phase carries with it no change regarding appropriate treatment, which should be as intensive or as sustained and always as vigorous as is indicated by presenting symptoms. But treatment should also comprehend procedure which adapts therapy in general to the ability of the individual to assimilate and react to remedies which are not alone potent for syphilis, but are capable of effecting a very toxic organotropism as well. Finally, this view in no wise interferes with the propriety of making blood and spinal fluid Wassermann tests at intervals, where circumstances permit. This, for the purpose of learning how these results square with the eventual outcome of neural syphilis. These observations may prove of prognostic value in years to come.*

But today, as regards an existing late luetic syndrome, enough time has elapsed since the introduction of the Wassermann reaction and comparison of its readings with associated clinical aspects, to prove that this test is not a reliable guide for treatment.

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*Aside from this, spinal puncture to learn if pleocytosis obtains and if so, to what extent, is important. The procedure from this standpoint may throw light upon or prove a valuable therapeutic indicator. However, the interpretation of spinal fluid cell count is beyond the province of this paper.

THE COLLOIDAL MASTIC TEST ON THE CEREBROSPINAL FLUID

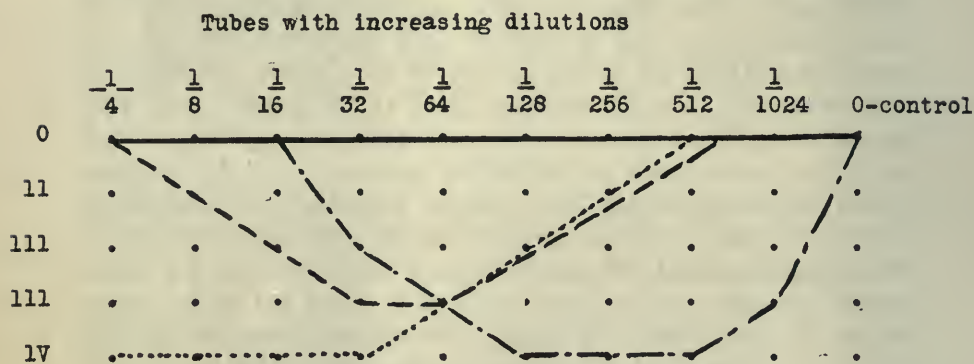
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THE use of colloidal gum mastic as a test for the spinal fluid was described by Emmanuel in 1915, as follows: A 10 per cent solution of gum mastic in absolute alcohol is used as a stock solution. As necessary for use, one c.c. is added to nine c.c. of absolute alcohol and this is "insufflated" into forty c.c. of distilled water. This gives a pearly, opalescent fluid. A 1.25 per cent solution of sodium chloride is made and $1\frac{1}{2}$ c.c. is put in a test tube and one c.c. is put in each of four others. To the first tube is added $\frac{1}{2}$ c.c. of the spinal fluid to be tested. After mixing the contents of this tube one c.c. is taken out and transferred to the next tube which is then shaken and one c.c. of this is transferred to the next and so on. None of the mixture is transferred to the fifth tube, which acts as a control, the extra c.c. in the fourth tube being discarded. In each tube there is then put one c.c. of the mastic emulsion and the tubes allowed to stand for about twelve hours. In this method the control tube shows a complete precipitation, but there is no precipitate in the other tubes, if the fluid is normal and the test negative. If the fluid is not normal, there will be a precipitate in some or all of the tubes in varying degrees.

Cutting found that by adding one part per hundred of a 0.5 per cent solution of potassium bicarbonate to the salt solution the contents of the control tube were not precipitated, but the precipitation in the other tubes was not affected. Apparently the results obtained by this modification of the test were more constant than by the original technic. In 1917, E. R. Smith published an important paper on this reaction. He used the test, as modified by Cutting, but carried the dilutions further, using ten tubes, and also described definitely the degree of precipitation: "One, denotes milky fluid, loss of opalescence and very slight precipitate; two, a distinct precipitate but with a milky supernatant fluid; three, a marked precipitate with slight cloudiness of the fluid above; and four,

complete precipitation of all the colloid." (Fig. 1.) The degrees of precipitation are definite, more easily recognized than the color changes in the gold-sol reaction and permit the plotting of curves, as is done with the latter reaction. (Chart I.) Smith reported the results of forty-five tests in which the mastic reaction and the gold-sol reaction were made on the same specimens of spinal fluid and from a considerable variety of cases of disease of the central nervous system. His most important finding was that the two tests gave practically identical results. Although not using both tests routinely, I have made a considerable number of observations of the mastic test on specimens of spinal fluid which were also tested by the gold-sol reaction and agree with Smith that the two reactions give practically the same curves and that they have the same diagnostic significance.



0 = no change; I = a milky fluid; II = a distinct precipitate but with a milky supernatant fluid; III = precipitate with cloudiness of the fluid above; IV = complete precipitation.

The solid line represents the normal; the dotted line, the type in paresis; the dash line, the tabetic; and the dot and dash, the nonsyphilitic.

In 1916 Urechia and Jorgulesci came to the conclusion that the mastic reaction and the gold-sol gave the same results but the mastic was less sensitive. They used the Emmanuel technic and reported their results as simply positive or negative. Sachs also used the original method except that he slowly mixed the alcoholic solution of the mastic with the water instead of "insufflating" it quickly as Emmanuel advised. By so doing he obtained a more stabile and less sensitive emulsion.

In 1908 Jacobsthal and Kafka published the details of their technic and also suggested that the varying degrees of turbidity or

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Fig. 1.—Illustrating the degrees of precipitation of the mastic. (After Smith.) No. 4 is on the left—complete; O—on the right.

precipitation in the tubes might be defined and used as ordinates, while the increasing dilutions were the abscissæ, as is done in the gold-sol reaction, and as Smith had previously done in the mastic reaction. They observed, as Sachs had done, that a slow mixture produced a more stabile sol, but also found that each sol has a salt sensitiveness which is not only individual, but changeable. In their method the 10 per cent mastic stock solution was kept 48 hours on ice before filtering and after that was kept in a dark flask, at room temperature. The admixture of the alcoholic mastic solution to the water was made very slowly, drop by drop, and using 60 sec. in the process and without shaking. After allowing the sol

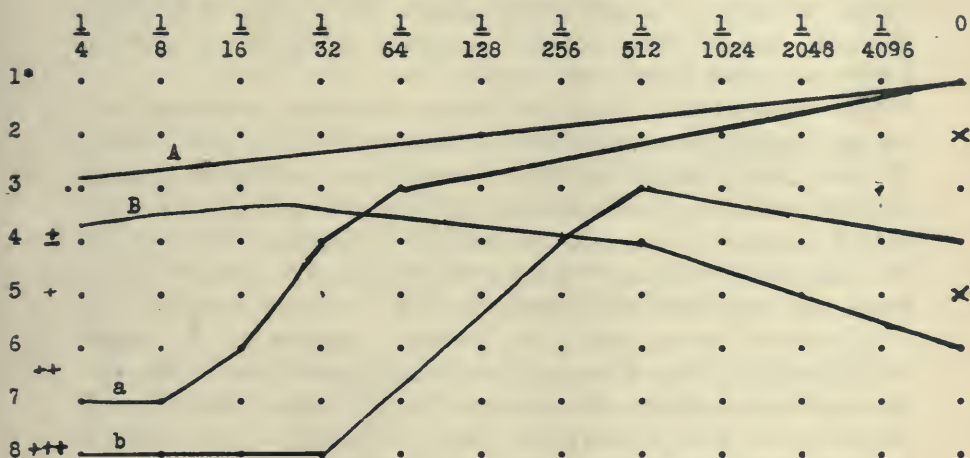


Chart II.—Chart of mastic curves with spinal fluid. (According to Jacobson and Kafka.) Nos. 1 to 4 indicate increasing degrees of turbidity; Nos. 4 to 8 increasing precipitation. Curves *A* and *B* are with normal fluid (*B* with the stronger salt solution). Curves *a* and *b* are with fluid from a case of paresis.

to stand for one-half hour at room temperature its sensitiveness to salt was tested by adding one c.c. of salt solution of increasing strength to each of a series of tubes containing one c.c. of the mastic sol. Two strengths of salt solution were selected: that which was added to the last tube that did not cloud and that which was added to the first tube showing a precipitate. The average value for the first ranged between 0.2 per cent and 0.9 per cent; that for the second between 0.6 per cent and 0.9 per cent, rarely going higher. After that, two series of tubes were prepared for the spinal fluid test, but in the first series the lower salt strength and in the second

the stronger salt strength were used in place of the fixed 1.25 per cent as in original Emmanuel technic. In this way two curves were obtained for each test. (Chart II.) Jacobsthal and Kafka defined the changes in the mastic sol into eight degrees, four differences in turbidity and four of precipitation, whereas Smith had defined only four degrees. From my own experience I should say that the division into four was preferable as being simple and easier to read. I have also observed the varying salt sensitiveness of mastic sol and it is certainly a source of error in the original Emmanuel technic but this difficulty seems to be overcome by the suggestion of Cutting which is used by Smith. The amount of shaking given to each tube, to mix its contents, should be the same in every case. A mixture of mastic and salt which will not precipitate if shaken twice often will when shaken four times.

These reactions are not in the nature of chemical reactions, but are apparently more in the nature of changes in the physical state. It seems quite probable that the Wassermann reaction belongs to the same order of phenomena, but in the present state of our knowledge it is useless to speculate too far in this direction. Much about the reactions of colloids is known, but much more remains to be found out, especially with reference to the biologic reactions. It would seem to me that this is not entirely a problem for the chemical laboratory. The clinician and the clinical laboratory has the opportunity to correlate the reactions with the other phenomena of disease and so perhaps cast some light on both sides of the problem. A sol of Berlin blue has been used for testing the spinal fluid, and I have found some interesting variations in the reaction of various other colloids to spinal fluid. Certainly anyone who could furnish an acceptable explanation of all of the phenomena observed in this connection would advance our knowledge of disease of the nervous system considerably.

CLINICAL RESULTS

In my clinical work with the mastic reaction I have used the method outlined by Smith. In most cases the general description of the curve is the same as the gold-sol curve which was made for the same specimen.

In *paresis* (22 cases) the mastic curve was invariably of the type 44443210 or 244432100. In all of these cases the gold curve also

was typically paretic except in one in which it was 1112221000, but in this case the symptoms and signs and the subsequent course of the case was that of paresis. The same type of curve was obtained in three cases of, so-called, optic tabes, and they had the same type of gold curve. In two cases, which were clinically tabes dorsalis when they were admitted to the hospital, the curve was the same as above, but their subsequent course justified changing the clinical diagnosis to paresis. The same curve was found in a case diagnosed as traumatic epilepsy in which there was considerable mental deterioration, but no signs of syphilis.

In *tabes dorsalis* (10 cases) the type of curve was found to be 012221000 or 1233210000 and there was very little variation between it and the gold curve.

In cases diagnosed as *cerebrospinal syphilis* (49 cases) the mastic curve varied considerably. In those in which the arteriosclerotic phenomena were alone present, the curve was several times flat (all 0). Usually it had the type 1122321000 or 0133200000. In several there was only a slight rise, 0011100000. In a case of syphilitic radiculitis it was 11333332210.

In cases of *cerebral arteriosclerosis* with no signs of syphilis (6 cases) the curves were 0011000000 or 0011100000. In no case was it flat.

In *spinal cord tumor* (3 cases) the curve was 0001222100, but in one of them it was 02333433310. In a case of syringomyelia it was 11222221110.

In *brain tumor* (9 cases) the curves varied widely, in three it was flat. In one it was 1221000000 although the gold was flat in that case. In one the spinal fluid was 0001221000 and the ventricular fluid was 0011123220 (tumor of the third ventricle). In a similar case the first portion of the ventricular fluid was colorless and gave the curve 0012432100, the second portion was yellow and gave a curve 00000012233210. The spinal fluid in this case was 0001100000. A glioma gave a curve 332100000.

In *encephalitis "lethargica"* (8 cases) three were flat. One gave a curve 012321000 and another 0001210000. The others were of the same type.

In *acute chorea* (3 cases) one, a febrile case, had a cell count of 12 and a curve 0112332100, the rest were flat.

In *Huntington's chorea* (2 cases) the curve was flat.

In *acute myelitis* (8 cases) the curve varied from 0122233210 to 000001222100. In a case with 000003444440 and a gold of 000000012321000 an operation was done in the thought that there might be a spinal cord tumor but nothing of the sort was found.

In *tuberculous meningitis* (2 cases) the curves were 000234430 and 0001124420. In neither case was the curve carried out to its conclusion apparently.

In *multiple sclerosis* (14 cases—3 with postmortem examination confirming the clinical diagnosis) the curve varied from 0001100000 to 112331000 or 001332100. In no case was it flat. In one case the gold-sol was 533310000 but the mastic on the same specimen was 112100000 and a repeated examination a week later gave gold 1233200000 and a mastic 1122100000. This agrees generally with the type of gold curve found by de Crinis and Frank and others, in multiple sclerosis.

Pernicious anemia associated with a *posterioro-lateral sclerosis* gave a negative or flat curve invariably (9 cases—3 with postmortem examination).

In *epilepsy*, 18 cases gave a flat curve. Two cases gave curves of the type 0001110000. In both of these a suspicion of brain tumor was present. In one associated with a fracture of the base of the skull the curve was 11221100000. In none of these cases were there any signs of syphilis.

The mastic curve was flat (the gold-sol also) in the following cases: *Lumbosacral arthritis* (2 cases). *Fracture of the spine* in the cervical region. *Traumatic conus lesion*. *Progressive muscular dystrophy* (2 cases). *Progressive spinal muscular atrophy* (3 cases). *Facial palsy* (2 cases). *Trifacial neuralgia* (4 cases). *Multiple neuritis* (4 cases). *Paralysis agitans* (6 cases). *Psychasthenia* (2 cases). *Hysteria* (4 cases). *Vasomotor neurosis* (4 cases—one a case of erythromelalgia).

As the result of my own observations it would not appear to me that the elaborate technical precautions used by Jacobsthal and Kafka in doing the mastic reaction are necessary to secure satisfactory diagnostic results although their experiments and observations are of great interest in connection with the general problems of the colloid reactions and the spinal fluid. The method described by E. R. Smith is entirely satisfactory from a clinical point of view. In the cases above cited the diagnosis was based on the

symptoms and clinical signs. In addition to the mastic and gold-sol reactions on the spinal fluid the Wassermann reaction was done on the blood and spinal fluid. The spinal fluid was also examined cytologically and with the carboic acid reaction of Pandi and the Nonne-Apelt reaction; and the amount of reducing substance estimated in every case. The following conclusions are based on a correlation of these findings.

CONCLUSIONS

The gold-sol test and the mastic test (Smith technic) give the same results and have equal diagnostic value. From the possibility of technical error it would be desirable that both should be tried routinely on the same specimen, although this will not eliminate errors due to faults in the collection of specimens—alkali in sterilizing the puncture needle, etc., or impurities in glassware, water used, etc. When they differ materially, it is my experience that the mastic reaction agrees more frequently with the confirmed diagnosis.

The colloid reactions are not tests for syphilis—they do not replace the Wassermann reaction. Cerebrospinal syphilis in all forms frequently gives a positive reaction, i. e., precipitate in some of the tubes, but a variety of nonsyphilitic organic diseases of the central nervous system produce similar results.

The comparison of the colloid reactions with the clinical diagnosis of cases may throw some light upon the nature of these reactions or their causes.

The chemical and physicochemical examination of the spinal fluid has as yet not shown any definite correspondence between these findings and the colloid reactions.

The colloid reactions are negative, i. e., no change in any tube in cases where there is no organic change in the nervous system, even though there is a severe disorder elsewhere either of metabolic or infectious character.

There is no parallelism between the colloid reactions and the amount of substance present in the cerebrospinal fluid that will reduce Fehling's solution. In a diabetic with six times the normal amount of this substance the colloid reactions were negative. In an arteriosclerotic with twice the normal amount it was slightly positive. In syphilitics with either decreased or increased amounts it is positive and so on.

In the diagnosis of the type of syphilitic affections of the nervous system the colloid curve is of suggestive value only, or else our ideas respecting these clinical types need revision. The former inference is the more probable, judging from the subsequent course of cases studied and their response to treatment. On the other hand, the relations of some of the sub types to the main types of clinical reaction may be changed, for instance: optic tabes, so called, is, according to the colloid test, more closely related to paresis than tabes, and this idea is borne out by the difficulties in obtaining any satisfactory result from treatment.

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SYPHILITIC AND TUBERCULOUS JOINTS

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THE clinical similarity between tuberculous joint disease and that due to inherited syphilis has been brought to the attention of the profession from time to time by the publication of case reports, but there has been no comprehensive presentation of such conditions by men having an abundance of material at their command. During the past four years I have observed over two hundred bone and joint cases which, while they possessed the symptoms usually ascribed to tuberculosis, were undoubtedly of luetic origin, and sufficient time has now elapsed to draw some conclusions from this work which may be of practical value.

The study was pursued with the purpose in view of noting the behavior of cases of this nature under proper therapeusis without mechanical protection, of discovering if possible clinical data by which they could be differentiated from tuberculosis, of seeking characteristic radiographic features and of determining the diagnostic value of the Wassermann reaction. The results as revealed in the cases reported below plainly show the need for a revision of our views concerning the diagnosis of chronic destructive joint lesions.

Most practitioners seem obsessed with the idea that nearly all chronic articular infections of the type under consideration are tuberculous. That inherited syphilis may be responsible for the symptomatology observed in a given case seldom enters into the discussion of its diagnosis, unless other stigmata of a luetic taint are frankly in evidence. This very common neglect of possible spirochetal infection is tersely summed up by Marshall, of London, who quotes a justly sarcastic remark of Fournier as follows: "In 1886 Fournier wrote, 'Everything which in a child or adolescent affects a bone, with the sole exception of traumatism, is ipso facto attributed to scrofula.' This is almost equally true at the present day, substituting the word 'tubercle' for 'scrofula.'"

The reason for this attitude of the profession is not difficult to

understand, but that it should be combated goes without saying. It must be remembered that, ancient as the disease syphilis is, its true pathology is of recent development, for the *Treponema pallidum* was not discovered until seventeen years ago, and even today, as Warthin puts it, "our knowledge of the pathology and symptomatology of the disease after the chancre and skin stage has been passed through is imperfect." Twenty years previous to the isolation of the spirochete Koch gave to the world the identity of the tubercle bacillus and there followed an outburst of pathologic research which proved, among other things, that this organism was very often responsible for the common form of articular disease variously known as "struma" or "scrofula." The presence of tubercles in a joint lesion was to the pathologists of a few years ago conclusive evidence that the Koch bacillus was the invading organism, for they were wholly unaware at the time that another and equally prevalent microbe, now familiar to us as the *Treponema pallidum* may produce tubercles identical in structure with those in which the tubercle bacillus is found. This imperfect pathologic conception naturally led to a faulty interpretation of clinical findings, and thus has come into existence the very widespread belief that chronic joint disabilities presenting a certain train of symptoms are tuberculous.

The error of this assumption will be obvious to those who are familiar with the modern pathology of syphilis. In both lues and tuberculosis an affected joint will present symptoms of articular irritation and there will be an attempt on the part of nature to prevent motion by means of muscular spasm. In both diseases there may be an indolent enlargement of the joint with effusion and the formation of pus, sterile on ordinary culture media. There will be sensitiveness, limp when a weight-bearing joint is involved, and alteration of attitude if the disease is vertebral. These manifestations are, of course, an indication that some pathologic process has attacked the joint structures, but there is nothing in them to even suggest the nature of the infection. The x-ray may show a bone lesion in either disease, but, contrary to accepted theories, there are usually no definite characteristics upon which to base a diagnosis. It might be expected that blood tests would afford a ready means of differentiating these diseases, but in a series of fifty of my cases the Wassermann reaction was so frequently negative in the

face of other evidence of syphilis, and satisfactory therapeutic results it may be said that in the late manifestations of inherited lues it is only occasionally of value.

It is interesting to note, by way of illustrating the undoubted similarity between the clinical pictures of these two diseases, that 51 of the cases of this series were diagnosed as tuberculosis by 26 experienced surgeons and treated on that hypothesis for periods varying from a few months to fifteen years. In the majority of these it was possible to obtain extremely suggestive evidence of ancestral infection or to find additional stigmata of an inherited taint. In some of them there were positive Wassermann reactions of from one to four plus, and in all of them there was a subsidence of active symptoms a few weeks after the exhibition of mercury and potassium iodide.

The behavior of these cases under drug treatment varied in the same degree that those of acquired lues may differ and conditions present at the first examination were no criterion of the progress to be expected. In many lesions of long standing response to mercury and potassium iodide was prompt and continuous. In others less formidable in their general characteristics, improvement dragged and symptoms did not disappear for a considerable time. The explanation of this lies, perhaps, in the fact that as most of the material was gathered in out-patient departments, the treatment was at no time "intensive" in the modern meaning of the term. Arsenical preparations were seldom used, and the results obtained were the effect of oral administration of the bichloride or protiodide of mercury and potassium iodide. It was the rule, however, that some improvement could be noted within two weeks. Occasionally a case would improve for a time and then come to a standstill. These were looked upon as tuberculosis appearing in a victim of inherited syphilis and were so treated.

The duration of the disease before treatment did not preclude the possibility of brilliant results. Two knee cases, one of six and the other of ten years' duration, recovered practically normal function, with regeneration of the necrotic bone areas. A spine case of fifteen years' duration, gained sixteen pounds in ten weeks. Three out of seven profusely discharging sinuses in this case closed completely and the secretion from the others became thin, watery, and of small volume. When the patient passed from observation, he was

able to take long walks and was leading a normal life. A hip case of twenty-five years' standing in which almost constant pain had been a predominant symptom, became entirely comfortable in about ten days. His Wassermann was positive. All these cases had been under continuous treatment for tuberculosis from the onset of their symptoms.

An instructive feature of this work was the frequency of relapses when the medication was omitted too soon after the patients became symptom free and the rapidity with which most of them again responded when the drugs were resumed. To prevent recurrence of the disease it would appear advisable to continue active therapy for at least a year after all symptoms have disappeared. It is the better part of wisdom to treat inherited syphilis just as thoroughly and persistently as the acquired type. The resistance of the spirochete to drug influence may be quite as great in the former as in the latter, which of course means that the spirilla can not always be controlled no matter what treatment is adopted, as in the case of a family of six, father, mother and four children, whose Wassermann reactions have remained positive for several years in spite of arsphenamine and mercury.

Certain facts in the general management of luetic joint cases have crystallized from my experience which may be worth recording. Of greater importance than all other measures combined is the vigorous use of those drugs known to have a specific influence on syphilis. Each case should be individualized. Routine prescribing and half-hearted dosage are to be condemned. Properly used, mercury, the arsenical preparations and potassium iodide may control the disease unaided, but common sense suggests that where weight-bearing joints are involved some form of apparatus should be used to protect the softened bone from pressure. For this purpose a splint which can be removed at night, together with crutches to prevent weight bearing, appears to be the best ambulatory device. The problem presented in cases of this nature differs fundamentally from that encountered in tuberculosis, and therefore plaster casts do not meet the indications. In the latter disease the desired end is an ankylosed joint, for it has been well proved that a little motion is dangerous, and there is no reason to expect repair of damaged joint surfaces and the return of practical function. In syphilis, on the other hand, the outlook for tissue regeneration

and restoration of useful function is not unpromising. It is well established that voluntary motion so far as the patient may be inclined to carry it out while lying down is not only devoid of harmful consequences, but is distinctly helpful in overcoming the stiffness which brace-wearing may induce.

Spine cases should be immobilized continuously until the radiogram shows complete repair. Here, too, braces have preference over plaster jackets, except in clinic cases, in order that the skin may be kept clean. Joints of the upper extremity are best treated by part time immobilization in light splints which may be easily removed and the patient encouraged to institute voluntary motion at stated periods after the acute symptoms have subsided.

These are the essentials of treatment and to them should be added the same attention to hygiene, fresh air and nourishment as is usual in the management of joint tuberculosis.

The appended case reports will illustrate the importance of a correct diagnosis in chronic destructive joint lesions and what may be accomplished in luetic infections. After a considerable experience with these conditions it is my firm belief that it is unwise to make a diagnosis of joint tuberculosis until the possible presence of inherited syphilis has been eliminated by five or six weeks of vigorous antiluetic treatment. The "therapeutic test" is still a valuable asset.

CASE REPORTS

CASE 1.—S. L. Age eight. Hospital diagnosis "tuberculosis of left hip;" duration of disease, seven months; previous treatment, plaster spicas; arc of motion 30 degrees with marked spasm. After two months of mixed treatment discharged from hospital with 90 degrees of motion, no pain or spasm, no apparatus. Remained well for three months without medication, then relapsed. Symptoms again yielded to hydrarg. chlor. corr. gr. 1-32 and potassium iodide grs. x, t. i. d. and did not reappear. Wassermann four-plus.

CASE 2.—G. S. Age ten. Hospital diagnosis "tuberculous hip;" duration seven months; symptoms moderate; radiograph showed acetabular disease; arc of motion 90 degrees. After four months of mixed treatment patient was symptom free and very active. Wassermann four-plus.

CASE 3.—D. H. Age six. Hospital diagnosis "tuberculous hip;" duration seven months; previous treatment, plaster spicas; arc of motion 20 degrees; hip extremely sensitive. After two months of mixed treatment pain had entirely disappeared and there was 90 degrees of motion in the joint. At the end of a year the lesion in the neck of the femur had regenerated. Wassermann negative. Father had syphilis before marriage and a positive Wassermann three years ago.

CASE 4.—M. C. Age four. Hospital diagnosis "tuberculous knee;" duration of disease two and a half years; previous treatment, plaster casts for two and a half years; condition at beginning of treatment, enlargement and tenderness of joint, ten degrees of motion with pain, considerable bone destruction shown by radiograph. After two weeks of mixed treatment there was marked improvement in pain and mobility. Three months later the child was symptom free. At the end of six months the joint was apparently normal except for some lateral instability due to bone destruction.

CASE 5.—E. L. Age five. Hospital diagnosis "tuberculosis of right elbow;" duration of disease three months; elbow swollen, painful and stiff at a right angle; radiograph showed involvement of the head of the ulna. After six weeks of mixed treatment pain and swelling had disappeared and there was 20 degrees of motion. Two weeks later there was 45 degrees of motion. At the end of a year there was voluntary extension to 170 degrees and flexion to 60 degrees. Radiograph showed considerable bone regeneration.

CASE 6.—H. E. Age four. Hospital diagnosis "tuberculous knee;" duration of disease one year; previous treatment, plaster casts. At the beginning of treatment knee was tender and swollen, the joint had about ten degrees of motion, child walked with limp and complained of pain. Two weeks later there was very noticeable improvement. At the end of three months the knee was practically normal with full range of motion.

CASE 7.—P. C. Age five. Hospital diagnosis "tuberculous left hip;" duration of disease four years; previous treatment, plaster casts and braces. Condition at beginning of treatment, left hip extremely sensitive, two discharging sinuses, one of three years' duration. Placed on mixed treatment August 17, 1917. Three weeks later pain had entirely disappeared. Oct. 17th the sinuses had closed and the boy was walking about the ward without protection to the hip, which was firmly ankylosed, and without pain.

CASE 8.—W. U. Previous diagnosis "tuberculous left elbow;" duration two years; joint ankylosed at a right angle; had been operated for abscess and lower end of humerus curetted. At the beginning of treatment the elbow was firmly ankylosed and a sinus had been discharging for two months. Four months later there was complete restoration of function. The Wassermann was negative, but the patient's sister, two years older, had a positive blood and three years later was sent to a hospital for the insane.

CASE 9.—F. F. Age twelve. For a year had all the symptoms ascribed to tuberculous hip disease. The joint was perfectly stiff, there were several profusely discharging sinuses, the boy was thin and sickly in appearance. After three weeks of mixed treatment a very striking improvement in his general condition was observed. In eight months he had gained twenty pounds in weight, he walked without limp, had 90 degrees of joint motion and the sinuses had closed except one which discharged slightly and closed permanently a few weeks later. When seen a year and a half after the beginning of treatment he was clinically entirely well.

CASE 10.—L. A. Age eleven. Hospital diagnosis "tuberculous knee;" du-

ration seven years; previous treatment, plaster casts; at the end of three years casts were omitted; symptoms returned and casts were again applied; omitted again after several months with same result. Had been without protection for three months when he came under observation. He then walked with limp because of pain and there was only 30 degrees of motion in the joint. He was placed on mixed treatment without protection to the knee. Four weeks later he was symptom free with normal joint function.

CASE 11.—H. F. Age thirty-one. Hospital diagnosis "tuberculous hip disease;" duration twenty-five years; active treatment for ten years; has had more or less pain ever since, which was particularly severe for several months before he was placed on mixed treatment Jan. 2, 1918. Nine days later the pain was very much less and the patient slept well for the first time in several weeks. Jan. 23, 1918, the patient reported himself as symptom free. Wassermann two-plus.

CASE 12.—F. P. Age four. Previous diagnosis "tuberculous left knee;" duration of disease, eighteen months; previous treatment, plaster casts and braces; condition at beginning of medication, knee swollen, tender, painful when used, marked limp, twenty degrees of motion. At the end of five weeks patient was discharged from the hospital walking without limp. He had no pain or tenderness of the joint and voluntary flexion to a right angle. He remained symptom-free for a year. After four months without medicine the knee again became stiff at an angle of 135 degrees, swollen and painful. Patient was given hydrarg. chlor. corr. gr. 1-32, and potassium iodide grs. x, three times a day. In four weeks he was again symptom-free except for limitation of flexion which was blocked at a right angle.

CASE 13.—C. B. Age eight. Hospital diagnosis "tuberculous right knee;" duration of disease six years; previous treatment, continuous immobilization in plaster casts. At the beginning of medication the knee was stiff, swollen and tender and had about ten degrees of motion. A radiograph showed a large necrotic area in the head of the tibia involving the joint surface. Patient was given hydrarg. chlor. corr. gr. 1-32 and potassium iodide grs. x, three times a day. Three weeks later the pain and spasm had largely disappeared and there was voluntary motion to nearly a right angle. Child has been symptom-free for two years and radiograph shows practically complete bone regeneration. One Wassermann was negative and another weakly positive.

CASE 14.—D. S. Age ten. Hospital diagnosis "Pott's disease;" duration of disease five years; previous treatment, plaster jackets, bone graft in spine and heliotherapy. When placed on mixed treatment this boy's condition was desperate. He was cachectic, had numerous discharging sinuses, had been bedridden for many months and death seemed but a matter of weeks. His response to the administration of mercury and potassium iodide seemed under the circumstances very remarkable. He gained rapidly in weight and color and in three months his sinuses had closed and he was able to take a few steps alone. Unfortunately at this juncture his mother took him from the hospital and he passed from observation.

CASE 15.—E. M. Age fourteen. Treated ten years for tuberculous knee,

wearing plaster or braces all the time. Radiograph showed necrotic areas in the head of the left tibia. When the patient came under observation the knee was enlarged and tender and had about ten degrees of motion accompanied by pain and spasm. She was given 1-32 gr. of hydrarg. chlor. corr. and 10 grs. of KI three times a day. The brace was continued two weeks, at the end of which time pain and swelling were considerably less and there was 80 degrees of joint motion. Brace removed and was not again worn. In three and a half months the patient was symptom-free and had nearly normal joint function. Family history and Wassermann both positive for syphilis. A year later radiographic examination showed regeneration of necrotic areas in the head of the tibia. There has been no return of joint symptoms. Wassermann two-plus.

LYMPHOSARCOMA AND SYPHILIS

By OSCAR BERGHAUSEN, M.D., CINCINNATI, OHIO.

(Received for publication, December 29, 1919)

THE lymph glands are so frequently enlarged in the syphilitic, that enlarged peripheral glands are always sought for in making the clinical diagnosis. The existence of lymphosarcoma and syphilis in the same patient is rather uncommon, therefore the writer feels justified in reporting two such cases. In the first case the general enlargement of the lymph glands was marked, but the marked enlargement of the spleen and abdominal lymph glands made the clinical diagnosis of lymphosarcoma rather easy. In the second patient the enlargement of the peripheral glands was so marked, involving chiefly the glands of the neck at first, that the probable diagnosis of Hodgkin's disease was made.

In both instances there was no question as to coexistence of syphilis; the patients admitted specific infection and the blood Wassermann reaction was strongly positive to different antigens. Anti-specific treatment was only of temporary benefit, proving of some value in the second patient, causing a decrease in the size of the glands of the neck but not preventing the gradual invasion of the entire lymphatic system. Since the luetic infection was still active, one might be justified in stating that the effect, lymphosarcoma, was due to the cause, syphilis, but probably the latter was merely a coincident infection. If we were acquainted with the real underlying cause, the stimulus which led to sarcomatous changes in the lymph glands, then probably we would be nearer to the cause of malignancy. As it is, we can merely assume that the syphilitic virus invaded the lymphatic system, and that sarcomatous changes resulted.

In the examination of the sections obtained before death, the typical textbook picture of lymphosarcoma was found in the gland removed from the abdominal cavity of the first patient; and changes described as being due to Hodgkin's disease were obtained from the superficial glands removed from the second patient, that is, large round cells and eosinophiles were numerous.

CLINICAL HISTORY OF FIRST PATIENT.—Mr. R. A. G. was referred to me on June 1, 1914, when the Wassermann reaction was found distinctly positive to two different antigens. The patient was a white man of about forty years of age. I saw him again on February 18, 1919, at the request of Dr. H. H. Wiggers. Seven months previously his abdomen began to swell. The superficial glands of the body were moderately enlarged. The spleen was greatly enlarged, firm and smooth. There was a large mass to be felt in the pelvis on the right side; other smaller nodules could be palpated. Vigorous antispecific treatment was given but the anemia persisted. The family wished everything done and consented to an exploratory operation and the use of radium. Dr. H. H. Wiggers performed the operation, but the removal of a single gland after the median abdominal incision was attended by so much hemorrhage that the wound was closed and the radium tube was not applied. The patient died soon after the operation.

Microscopic sections prepared from the single gland were examined and diagnosed as lymphosarcoma, having the appearance of uniform lymphoid tissue composed of a cellular reticulum in which small round cells were embedded.

CLINICAL HISTORY OF SECOND PATIENT.—Mr. J. S., white male, aged forty-seven, salesman, complained of weakness and "lumps" on the body. His father had died of tuberculosis at forty-five; mother still alive at seventy-nine. Three brothers and two sisters died of tuberculosis. The patient's wife had one miscarriage; one healthy child aged eleven years. He had the ordinary diseases of childhood; was always well except that he contracted lues at age of twenty. Later his health began to fail him, so he secured a position which kept him in the open air a great deal; he drove a bakery wagon and later became a salesman. He never used alcoholics to excess.

His present trouble began in 1918, when he lost his appetite and became weak. The first physicians whom he consulted told him that he had tuberculosis. He was finally seen by Dr. Stephen Cone who suspected the presence of lues, and had me see him on March 31, 1919. At this time he was suffering from multiple glandular enlargements which were diagnosed as Hodgkin's disease although the Wassermann reaction was strongly positive. Dr. Cone then gave him a series of arsphenamine injections, the patient improved in a general way, the glands became smaller. He later lost weight again and was sent to the Cincinnati Hospital.

The glandular swellings began at the angle of the left jaw many years ago. He thought that it probably was due to an abscessed tooth. It was not painful. Some twelve months ago another lump came on the other side. Both began to enlarge. The superficial glands of the neck, chest, and groin began to enlarge, some reaching the size of a large walnut. The patient had lost 40 to 50 pounds during the year. His appetite had improved after the salvarsan injections. Nevertheless, there was a diffuse pain over the abdomen and left buttock. He has dyspnea on exertion, attacks of syncope before taking the salvarsan but none now, no edema of the extremities. No coughing, no hemoptysis. At one time he suffered from polyuria.

PHYSICAL EXAMINATION, OCTOBER, 1919.—Fairly well developed, somewhat emaciated, anemic, apparently in no great discomfort. The mucous membranes of the mouth were pale, the teeth in poor condition, the tonsils enlarged. The

pupils were unequal, the right one contracted. The left one reacted normally to light, the right not at all. Both react to accommodation. No ptosis nor evidence of facial paralysis, the tongue protrudes in the middle line, the angles of the mouth are not drawn.

The glands of the neck were greatly enlarged, both posteriorly and anteriorly to the sternomastoid muscles. The enlargement of the glands extends down into the supraclavicular fossæ and into the axillæ. The whole chest was emaciated, with numerous small nodules on the anterior wall; three on the posterior aspect of the right chest. The abdomen was thin and had similar nodular masses, especially in the left iliac region. The tip of the spleen was readily palpable below the costal margin, smooth and firm. Distinct nodular masses within the abdomen could be felt. The glands were enlarged in the groins, and along the lymphatic channels of the lower extremities. There was no evidence of paralysis or other abnormalities. The knee jerks were markedly exaggerated on the right side; plantar reflexes normal, no Babinski. Arm reflexes exaggerated. The patient walked with a limp owing to pain in the left buttock; no ataxic gait. The patient has had bleeding hemorrhoids.

The examination of the lungs showed no areas of impaired or relative dullness. Posteriorly a few small, moist rales over the bases. The apex beat of the heart palpable in the 5th interspace, $7\frac{1}{2}$ cm from the midsternal line. The left border of the heart measured 9 cm. from the midsternal line in the 5th interspace; the right border measured $2\frac{1}{2}$ cm. from the midsternal line. There were no murmurs over the precordium; the first sound was strong and booming and slightly roughened; the second sound was not accentuated. There was no arrhythmia. The systolic blood pressure measured 126, the diastolic 86. The vessels showed evidences of arteriosclerosis. The red cells numbered 3,580,000 on Oct. 28; the Hbo., 45 per cent; the white cells, 7,350 of which 73 per cent were polynuclears, 1.5 per cent eosinophiles, 3 per cent large and 18 per cent small lymphocytes, 1.5 per cent transitionals, and 3 per cent myelocytes. The red cells were irregular in size.

The abdominal pains became worse, blood was found in the stools, the patient developed symptoms of internal hemorrhage, and died on Nov. 7, 1919.

NECROPSY REPORT.—The body is that of an emaciated white man. Rigor mortis is present, lividity is scarcely marked. The finger nails are livid. The pupils are equal. There is no peripheral edema. The abdomen bulges so that the abdominal surface is above the surface of the thorax. Palpation shows no evidence of fluid in the abdominal cavity. In the neck on both sides, but most marked on the right, are masses, nodular, firm and apparently made up of collections of enlarged lymph glands. Scattered throughout the body, particularly on the abdomen and thorax just beneath the skin and not adherent to it for the most part, are very numerous single and agglomerated enlarged lymph glands, similar in feel to the smaller ones in the neck. In the left groin is a large mass of such lymph glands. In the right groin the glands are discrete and movable. Under the skin on the anterior surface, these enlarged glands vary in size from that of a BB shot to larger ones several centimeters in diameter. About the middle of the left thigh between the abductor muscles, the adductor longus

and adductor magnus, is a small lymph gland, measuring about 1 cm. in diameter.

When the body is opened one finds between the muscles, following the lymphatic distribution and between the pectorals, numerous small and large lymph glands similar to those felt beneath the skin. These glands are cartilaginous in appearance, but not so firm, and show no evidence of macroscopic necrosis.

When the abdominal cavity was opened, the bowels were found distended with gas for the most part and also some of the loops of the small intestines and cecum apparently are filled with brownish fluid, filling the lower part of the abdominal cavity in the pelvis, although there is very evident dulling of the peritoneal surface of the loops. The upper loops of the bowels, however, are slightly dulled but to them the omentum is not adherent. Covering the diaphragm and binding the diaphragm and liver together by recent fibrous adhesions is a large amount of fibrinous exudate, that is moderately adherent to the liver and to the diaphragm as though it were beginning to organize.

There is a slight increase in fluid in both pleural cavities but this is clear and there is no evidence of pleuritis. The anterior mediastinum is occupied by numbers of discrete and conglomerate enlarged glands which, however, have the same appearance as the smaller ones beneath the skin and in the axillæ. A larger mass of enlarged glands just over the base of the heart measures $6\frac{1}{2}$ cm. in greatest diameter. The posterior mediastinal glands are involved in the same fashion. The hila of the lungs are filled with tumor masses, and the great vessels at the base of the heart are surrounded by them. Occupying the space beneath the arch of the aorta and extending from the arch downward to the diaphragm around the esophagus is a large mass of glands, some larger than one's fist. As one dissects out the organs of the neck, one sees that trachea and esophagus are involved in the process.

The omentum contains one large collection of enlarged lymph glands and some smaller ones. Some larger masses are more sclerotic than others and show some evidence of contraction and almost of umbilication. None of them however show any macroscopic necrosis. Practically all of the mesenteric glands are involved. Just below the gall bladder and walled off with recent adhesions, is a large pocket of thick yellowish pus. Apparently all the retroperitoneal lymph glands are enlarged, united together into large and small nodules and the huge mass formed in this way is adherent to the transverse colon, both the flexures and to the stomach and spleen.

In removing the liver, a small opening to the stomach wall, 1 cm. long and about 2 cm. wide, with necrotic edges, is encountered in the lesser curvature below the cardiac orifice. From this there is oozing of grumous material. In the stomach is an opening and it appears that the walls are studded with indolent peptic ulcers that measure $2\frac{1}{2}$ cm. to 6 cm. in diameter, with firm edges, grey bases, and sharp walls. The large ulcer which has perforated seems from the feel to have occurred in a mass of tumor tissue which has ulcerated and perforated. It is possible also from the feel that the other ulcers have originated in the same way, for at two points beneath the mucous membrane, a couple of inches from the pylorus there are submucous nodules measuring about $1\frac{1}{2}$ cm. in diameter which are adherent to the mucous membrane but not adherent to the

submucosa and at the apex of one of these is a small superficial, indolent ulcer.

Both kidneys are completely surrounded by tumor mass. In the left kidney, the pelvis is filled with a large tumor mass. In the duodenum are small clots of blood. Otherwise there is nothing unusual in the duodenum. The adrenals seem to be healthy.

The spleen itself, though anemic, is healthy and is intimately adherent to the liver, and in its substance there is one tumor mass.

The lungs show a well-developed edema, and throughout the substance of each are very small nodules about the size of a pinhead, which, on section, seem to be areas of bronchi surrounded by a malignant infiltration. There are also scattered areas here and there of larger nodules, which, on section, prove to be typical metastatic growths; one of these measures at least $1\frac{1}{2}$ cm. in diameter.

The heart is small, flabby, and gray. There are no valvular defects and but a moderate amount of fibrosis of the papillary muscles. The aorta throughout its whole length is mottled with intense fatty degeneration and scattered here and there throughout its length are pearly succulent patches of active syphilitic aortitis. Just at the region of the celiac axis the aorta is completely surrounded and compressed to form one-half to two-thirds its natural size by a collection of tumor nodules.

The liver is small, gray, and except for the presence of fibrinous exudate on its surface, shows nothing unusual. The gall bladder is distended with bile, due in part, apparently, to the presence of tumor masses and lymph glands along the ducts. The right tonsil is completely replaced by a tumor mass that had all the characteristics of the growths on the body. The thyroid was not involved, but was compressed by the mass lying above it.

The kidneys are about of normal size, but extremely pale and cloudy. There is no other lesion of the genitourinary tract. In other words, the whole picture is one of apparently complete involvement of the lymph nodes of the body, particularly of the neck and trunk, in a malignant process. The bone marrow also is of the lymphoid type.

ANATOMIC DIAGNOSIS.—Lymphosarcomatosis; gastric ulcers, one of them perforating into the general peritoneal cavity; acute fibrinopurulent peritonitis; luetic mesaortitis; hemorrhage from the gastric ulcers; anemia.

MICROSCOPIC EXAMINATION.—

Lymph Glands.—Show complete replacement of lymphoid structure by an endothelioid type of cell with large nucleus. There are numerous giant cells with both single and multiple nuclei of the type described ordinarily in connection with Hodgkin's disease, of the Dorothy Reed type. There are also many eosinophiles in the glands. Some of the glands show marked sclerotic changes, being identical in appearance with the later changes described as Hodgkin's disease. Others show much less connective tissue. There are very many mitotic figures in the tissue.

Liver.—The liver shows diffuse infiltration with cells of all the types seen in the lymph glands, some of these cells being especially large, with very darkly staining nuclei. No nodules or collections of such cells are seen. There is a marked central necrosis with fatty degeneration.

Stomach.—Cross section of one of the ulcers shows the mucosa infiltrated in places with cells resembling those in the lymph glands. Toward the central portion of the section the mucosa is replaced by tissue like that described in the lymph gland. The central edge of this tissue is necrotic and broken down irregularly.

Lungs.—Metastases of somewhat different sort of tissue in the lung in the immediate vicinity of the large veins and elsewhere. Here the cells are smaller, practically all of the same size. No eosinophiles or giant cells are seen. Here tissue like a true metastatic sarcoma is found.

Spleen.—The spleen is not replaced as are the lymph glands, but the structure is left intact, with, however, a diffuse infiltration of all the types of cell described as being in the lymph gland.

Aorta.—Luetic aortitis.

Kidneys.—Marked degenerative changes: fatty.

An important thing is that while the lymph glands and stomach ulcer show lesions described as characteristic of those of Hodgkin's disease, the other metastases are characteristically round-cell sarcoma.

In conclusion I wish to thank Dr. Paul G. Woolley, Pathologist of the Cincinnati General Hospital, for permission to publish his necropsy report of the second patient.

SYPHILIS OF THE PROSTATE*

By LOYD THOMPSON, M.D., HOT SPRINGS, ARK.

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INTRODUCTION

THAT syphilis of the prostate should be considered rare is most justifiable from a perusal of the literature dealing with the subject. Practically all textbooks on syphilis and diseases of the genitourinary organs pass over involvement of this gland in the syphilitic process, either without mention or with only a cursory remark that it is a most rare condition, possibly quoting one of the few cases which have been reported.

It, therefore, seems opportune at this time critically to review the literature on the subject and report a personal observation.

HISTORICAL AND CRITICAL REVIEW

The early syphilographers apparently did not recognize the condition, and even such an astute observer as Astruc¹ failed to see it. The same may be said of those distinguished syphilographers of the latter part of the eighteenth and early part of the nineteenth centuries; namely, Hunter,² Benjamin Bell³ and Swedieur.⁴

However, according to Lancereaux,⁷ Jean-Louis Petit (1674-1750) at a considerably earlier date supported the view which attributed a syphilitic origin to a certain number of prostatic tumors. But, as Lancereaux points out, Petit in common with other authors of his time, confounded syphilis and gonorrhea.

In 1836 Rattier⁵ reported a case which was later also reported by Ricord,⁶ in which at autopsy the prostate, along with other genitourinary organs, was found diseased. It has been alleged by certain writers that this case as reported by Ricord was one of syphilis of the prostate.

*This is the second of a series of articles dealing with the urinary organs and the genital organs of the male. The first, Syphilis of the Bladder, appeared in the January, 1920, number of this Journal and the others will appear in subsequent numbers.

OBSERVATION I, RATTIER,⁵ 1836

A man of 52, who had suffered from gonorrhea on four different occasions, the dates of which being uncertain. On admission to the hospital he was suffering from an orchitis and hydrocele. The latter was punctured by Ricord, but reappeared in three days, when it was again punctured. In a short time the patient left the hospital cured of his orchitis and hydrocele, but with a prostatic urethritis. However, he soon returned with his condition as when first admitted. The hydrocele was again punctured by Ricord, but the gonorrhea continued to progress and death followed. The autopsy revealed a large ulceration which had destroyed three-fourths of the urethra; several large rounded ulcers of characteristic venereal formation affecting all the coats appeared on the surface of the bladder. The prostate was profoundly involved and in the rear a flap of the urethra adherent to its base was detached from the surrounding parts.

Although, as stated above, this case has been considered one of prostatic syphilis, it seems that the evidence is entirely too meagre upon which to base such a diagnosis.

In 1851 Ricord⁶ reported in his *Traité complet des maladies vénériennes* the case which has just been quoted, and another case in which at autopsy the prostate was found to be diseased and which also has been considered one of syphilis of this gland.

OBSERVATION II, RICORD,⁶ 1851

A man of 18, who had contracted a chancre of the frenum some days following a suspicious intercourse. The sore spread from place to place, encroaching on the meatus, and in a short time an abundant discharge developed, with painful urination. For three months the discharge persisted, with pain and incontinence of urine, followed by death from marasmus. The autopsy revealed an ulceration of the meatus which had encroached upon the urethra and a second elongated ulceration in the membranous and prostatic portions. The prostate was the seat of a vast ulceration having the character of a phagedenic chancre. The lateral lobes of the prostate were replaced by two large, irregular excavations communicating with each other. The neck of the bladder was partly destroyed, while the walls were hypertrophied and the mucous membrane ulcerated and covered by elevated tumors.

This case has been accepted as one of syphilis of the bladder,⁹ and although the evidence is not absolutely conclusive, it seems that it should also be accepted as one of syphilis of the prostate.

Although Lancereaux,⁷ whose great *Traité de la Syphilis*, published first in 1866, and which is even today a model of excellence, both as to the observations of its author and particularly as to the careful bibliography, failed to quote Ricord's case, he was of the

opinion that syphilis could attack the prostate. This opinion was based upon the existence in a case which he stated was to be given further on of a change in the gland to which it would scarcely be possible to attribute any other than a syphilitic origin. However, a careful perusal of all the cases cited in Lancereaux's book fails to reveal any mention of prostatic involvement, so if this great syphilographer did observe prostatic syphilis, it is impossible to include his case in the present study.

Reliquet¹⁰ in 1885 reported a case before the Medical Faculty of Paris, which is quoted by most authors on the subject as one of syphilis of the prostate.

OBSERVATION III, RELIQUET,¹⁰ 1885

A man of 28, who had suffered from a chronic urethral discharge for many years, upon urination passed small white particles like sputum, which were homogeneous in consistency and yellow in the center. He had had various recurrences of hematuria, always preceded by very violent pain on urination, especially at the end of the act. He also had an orchitis on each side. He confessed to many attacks of gonorrhea, the first one lasting seven or eight years, but had never been completely cured. Upon examination, the testicles were found enlarged, the epididymis indurated, and the cords were large as far as the inguinal canal. The surface of the testicles was not regular, and pressure caused characteristic pain. Rectal examination revealed the prostate large and harder than normal and presented a mass projecting on the right side. There was no stricture in the urethra, but upon passing a sound, the urethra was very tender in the deep portion and at the neck of the bladder. After observing the patient carefully Reliquet arrived at the conclusion that the primary affection of the deep urethra kept a constant appearance of swelling of the epididymis and the cords and he proposed deep injections, which were accepted. The method of Mercier was employed with a solution of silver nitrate of 2 per cent. These injections were continued for many months, with little benefit. The patient had been questioned many times concerning syphilis, but always denied it. One day Reliquet observed behind the eye at the root of the hair a very characteristic syphilitic papular eruption. Bazin agreed in the diagnosis and he and Reliquet fastened upon the disease of the testicle and prostate a diagnosis of syphilis; antisyphilitic treatment and two seasons at Luchon confirmed the diagnosis and cured the patient.

The above case, while presenting some features which throw some doubt on the diagnosis of syphilis of the prostate, nevertheless seems to present enough evidence to warrant its acceptance as such.

For the next case purporting to be prostatic syphilis we must

turn to the Polish literature, and find that Wroczyński¹¹ in 1894 reported such a case.

OBSERVATION IV, WROCZYŃSKI,¹¹ 1894

In 1890 S. came to Wroczyński complaining of obstruction in defecation. Upon investigation a tumor was found in the rectum above the internal sphincter, which compressed the lumen of the rectum. The tumor was hard, not painful, lay directly in the prostate gland, and exerted pressure on the urethra, for which reason the bladder was emptied with difficulty. No disturbance in the internal organs. Patient was 32, and had had syphilis 14 years previously. No relapses after treatment. He was married and had three healthy children. Considering that there had been a relapse of syphilis, potassium iodide was prescribed. Under this treatment the patient's condition became worse, the tumor enlarged, closing the lumen of the rectum. Patient lost 18 pounds; became neurasthenic. Presuming cancer, the patient was sent to Warsaw for operation: in Warsaw it was diagnosed as malignant rectal tumor, inoperable. In order to satisfy the patient, however, he was treated with mercury, and after six years was well.

Inasmuch as the tumor in this case did not respond to potassium iodide, in fact, became worse, and furthermore although the author states that the patient was well after six years he does not state the condition of the tumor or the amount of mercury administered, it seems to be doubtful at least that he was dealing with syphilis of the prostate.

OBSERVATION V, GROSLIK,¹² 1897

On December 11, 1893, a man of 43, who had complained for ten days of pains in the perineum which were aggravated upon urination, appeared for examination. Urination was frequent and flowed only drop by drop. A few years previous the patient had suffered from gonorrhea which lasted for a long time. Syphilis was denied. The patient was pale, the features pinched, pulse accelerated, temperature normal, nutrition good. There was a feeling as of a foreign body in the rectum. Upon stripping the urethra, a drop of purulent fluid appeared at the meatus and was found to contain pus and red blood cells, but no gonococci. Rectal examination showed a voluminous mass on the anterior wall of the rectum and in the position of the prostate. This mass was the size of the fist of an adult, very hard, irregular, tender and painful, especially on the right side. The mass was immovable, and the upper border could not be reached with the finger. The patient was treated with morphine by mouth, two baths daily, enemas, belladonna suppositories and milk diet, under which treatment the symptoms somewhat improved, although there was no change in the prostate. At this time the diagnosis of carcinoma of the prostate was made and the patient discharged as incurable. A few days later it was learned that he had

suffered from a typical chancre on the glans and went through secondary manifestations of syphilis, for which he was treated with inunctions of mercury. A diagnosis of gumma of the prostate was therefore made and mercury inunctions and potassium iodide internally were begun. In consequence of this treatment the prostatic gland rapidly decreased in size, and in four weeks there was no enlargement. The bladder and urethra disturbances also had disappeared, the patient urinating normally. However, after a few months, the patient reappeared with the same symptoms and approximatedly the same findings in regard to the prostate. Once more antisyphilitic treatment was repeated, the symptoms disappeared rapidly and in three weeks the gland became normal. In September, 1894, another relapse occurred, at which time also the prostate was large and hard, and again, under antisyphilitic treatment, the symptoms disappeared quickly.

There seems to be no doubt that this case was one of syphilis of the prostate and is accepted as such.

OBSERVATION VI, ROCHON,¹³ 1897

A man of 50, in good health, who had not had gonorrhea since the age of 20. At the age of 4 he had an abscess on the right thigh, which lasted for six months. For eight days he had urinated with great difficulty and had a feeling of unpleasantness in the perineum and in the rectum. In the evening he had had a violent chill and intense fever, with pains radiating from the loins and perineum. Only a few drops of urine could be evacuated and this with great difficulty. The following day he had retention of urine, which necessitated catheterization, at which time one litre of urine was withdrawn. Rectal examination revealed the left lobe of the prostate almost normal but the right increased in size, hard, and painful. The following day he was again catheterized there or four times, and the left lobe of the prostate was now somewhat enlarged. This condition continued about the same until February 8, when it was learned that ten years before he had had a lesion on the penis and four years later abscesses on the buttocks, which were cured rapidly after iodides had been used. He was therefore placed upon inunctions of mercury and potassium iodide in four gram doses daily, and by the 5th of March a complete cure had resulted.

The evidence in this case seems entirely too meagre upon which to base a diagnosis of prostatic syphilis, although, of course, the possibility must be admitted.

OBSERVATION VII, DROBNYI,¹⁴ 1906

On the 6th of June, 1905, P. F., a cavalry officer, aged 32, was seen by Drobný and complained that three months previously he began to notice pain in the lower part of the abdomen, somewhere inside, upon ejaculation of the semen. Pains at first were insignificant, but gradually increased, and latterly reached such a degree that coitus became tormenting. There was no pain when quiet, or at first on horseback riding, or when riding in a carriage; under those conditions he felt but little discomfort. There was pressure in the rectum, as if a call for

defecation. Secretion from the urethra never appeared. Urination was more prolonged than formerly, but painless; the urinary stream a very long one. Urination was somewhat oftener than formerly; eight to nine a day; at night time at least one or two.

The patient had syphilis at 20, for which he was treated only the first year, (68 inunctions with mercury). No further treatment after that. Never had gonorrhea.

Examination revealed: nutrition below normal, spare; pale skin, with yellow shade. Hair sparse on the head. All glands enlarged, especially those under the right axilla, and of the neck. Bones normal. Teeth bad: 9 ulcerated, 2 wanting. Heart, lungs, digestive organs, normal. Liver, somewhat painful; spleen, normal. Pars pendula penis, normal. Testicles, well developed, but hang down somewhat. Slight varicocele of left spermatic funiculum. Cremasteric reflexes increased. Urethroscopic investigation showed nothing abnormal in the canal. Bougie No. 17 meets with obstruction in the neck of the bladder. On examination per rectum the prostate was found enlarged to the size of a hen's egg, the right side being considerably larger than the left, smooth, hard, somewhat painful. Pressure on the prostate caused call for defecation. With light massage there was pressed out a cloudy liquid, colored somewhat yellow, about 3 to 4 drops. Microscopic investigation disclosed the presence of a small quantity of pus corpuscles in it. No microorganisms found. Urine, normal; no admixture of either pus or blood in it.

Diagnosis of syphilis of the prostate, in view of the absence of data for chronic prostatitis, prostatic hypertrophy, tuberculosis, or tumor.

Treatment with injections of mercury salicylate, with a solution of arsenic and 10 per cent iodipin, a teaspoonful three times a day.

On September 15 the patient was discharged, well. December, 1915, he wrote that he was feeling well, and had gained eighteen pounds in weight.

The evidence in this case seems sufficient upon which to base a diagnosis of syphilis of the prostate, although Drobnyi does not state that the prostate had become normal at the close of the treatment.

OBSERVATION VIII, KUDINTSEFF,¹⁵ 1908

CASE 1.—A man of 59, who, when 23 years old, had syphilis, and was treated for three years. At 30 was married and had healthy children and grandchildren. The patient complained of painful and frequent urination; had become weak because of constant pain, thin, and unable to perform his duties.

On objective examination there was evident decided loss of flesh, and the general appearance was one of cancerous cachexia. The urinary stream was sluggish, falling at the feet; 50 to 60 c.c. of urine at one urination, with 100 c.c. remaining. In the urine there was much mucus, and a few bladder epithelia, otherwise normal. On direct and combined examination of the prostate an inconsiderable hypertrophy of its lateral portions was observed, and a considerable hypertrophy of its middle portion, protruding into the lumen of the bladder; the prostatic portion

of the urethra was about 10 cm. long. Tenderness and pain, on examination of the prostate and bladder, even instrumental, not considerable, which was considered very significant, since examination of the prostate is usually very painful, especially if instrumental.

Diagnosis: gumma of the prostate. Treatment: 20.0 KI in two weeks.

A year after treatment: urine normal, urination 6-8 times daily, bladder being completely empty. Prostate slightly enlarged, reminding one of chronic catarrhal prostate.

CASE 2.—Patient of 62, who denied syphilis, consulted Kudintseff October, 1906. For months he had suffered from disturbed urination, having frequent calls, painful, both day and night. Dr. A. A. Belts stated that he had treated the patient the last two months, conditions improving under treatment, but returning when treatment stopped. Urine cloudy, alkaline, 1.017 sp. gr., with small sediment; on microscopic examination: pus corpuscles, red blood corpuscles, bladder epithelium; no neoplastic elements. Patient fairly well nourished; considerable exhaustion noticed; neurasthenia; even symptoms of depression of the central nervous system: distraction, forgetfulness, inattention to official duties, which he formerly performed with care. Thoracic and gastro-intestinal organs normal. Examination of the genitourinary organs; Charrière's bougie No. 24 passed with ease through the urinary canal, prostatic portion lengthened and somewhat bent; some pain on passing of bougie. On rectal examination the prostate was enlarged and painful on the right side, being twice the size of the left side, which was normal. Cystoscopy: evident trabecular catarrh of the floor of the bladder; in the region of the left trigonum, less than 1 cm. from the orifice of the right ureter, a small ulcer, of irregular, round contour visible, the largest diameter being about 1 cm., with cut edges and dirty bottom, whither also was drawn part of the bladder wall in the shape of a tumor, with very hyperemic mucosa, raspberry color, in the direction of the right portion of the prostate.

The absence of polyuria, absence of different frequency of urination day and night, unilateral hypertrophy of the prostate, was thought to be against its senile hypertrophy. Cancer was thought of, but the small pains on instrumental examination and absence of hemorrhage when ulcer was already present in the bladder, was against carcinoma. Lues was thought most likely, notwithstanding all denials. Gumma localized in the lateral portion of the prostate. Its size not less than that of a pigeon's egg.

Treatment with KI for three weeks, then Zittmann's decoction. Gradual improvement. After 6 months; ulcer completely healed, the cystoscope showing only a fresh cicatrix in its place; prostate gland normal in size; micturition normal and painless.

In a note is added:

A case similar to Case 2 was at that time under observation by Kudintseff and Dr. M. A. Frenkel—namely a case of gummatous prostate of the right portion.

Patient 57, with dysuria symptoms, reminding one of senile prostatism.

Absence of polyuria, partial hypertrophy, inconsiderable pain, on examination with cystoscope (without local anesthesia) compel one to suspect lues.

Although the patient categorically denied lues, but from the anamnesis,

(abortions, children born dead, etc.,) it was evident that he was a syphilitic. He was, therefore, treated accordingly. After three months under treatment of KI and with decoction of sarsaparilla the patient was almost well. No subjective complaints of disturbed micturition, prostate normal; swelling of right portion almost unnoticeable. The patient was still under observation.

In the first of Kudintseff's cases there seems little justification for the diagnosis of syphilis of the prostate, but in the second case such a diagnosis seems entirely warranted. In the case which is added in the note and which was still under treatment at the time the paper was written, there are not enough data from which to draw conclusions. It is therefore not accepted as one of prostatic syphilis. It must be added that the age of each of Kudintseff's cases was such that nonspecific prostatic hypertrophy might be expected.

OBSERVATION IX, POWER,¹⁶ 1908

On November 4, 1902, Power saw a man of 54, who stated that in January, 1902, he began to have difficulty with urination, which soon compelled him to arise many times during the night. He also complained of pain in the right testicle and in the perineum. He gave no history of syphilis, but admitted gonorrhea at the age of 20. Upon examination he was found to be garrulous and full of highflown ideas as to his future prospects. Urination was normal and the urine was free from albumin. The prostate was found to be uniformly and greatly enlarged, very hard and from its midpoint a hard and firm band extended upwards toward the right side. Suprapubic prostatectomy was performed on November 11, the prostate being removed piecemeal and with very great difficulty, owing to the density of the adhesions by which it was attached. The pathologic report stated that "the microscopic sections show no malignant growth and no adenoma. It is probably a simple hypertrophy of all the constituents of the gland." On November 27 the patient urinated naturally. The wound was healed on December 1, but broke down again on December 5. He then had an attack of double orchitis, which ended in the formation of a gumma of the right testicle. The gumma softened and an abscess was opened on January 5. Both testicles cleared up rapidly when iodide of potassium was given. The patient left the hospital much relieved, without pain and with no frequency of urination. A few weeks later the patient applied again for relief of the gummatous periostitis of the forearm, which was also quickly cured by potassium iodide. Power states that he saw the patient frequently during the next three years and that his bladder symptoms were relieved, the urination being normal.

There seems to be little or no reason to call the above case one of syphilis of the prostate, particularly in view of the age of the patient and the report of the pathologist, which was to the effect that the condition was probably one of simple hypertrophy.

OBSERVATION X, DIVARIS,¹⁷ 1908

A patient, aged 34, complained of frequent urination, chiefly at night, leading to broken sleep, much pain, urethral discharge, difficulty in passing water, and at the end of urination the passage of urine tinged with blood. Rectal examination showed the existence of an enlarged prostate which did not present any nodules. A diagnosis of tuberculous disease of the prostate was made and the patient was ordered to take cod-liver oil and was treated with instillations of corrosive sublimate and injection of nitrate of silver. No improvement occurred and, although the patient denied syphilis, he was put upon an antisyphilitic course consisting of injections of biniodide of mercury and iodide of potassium. A month later he was quite well.

The evidence in this case is entirely too meagre to warrant the diagnosis of syphilis of the prostate, particularly inasmuch as the condition of the prostate at the close of treatment is not stated.

OBSERVATION XI, DESNOS,¹⁸ 1910

CASE 1.—M. H., 53 years of age, who had had gonorrhea at 22, which lasted eight or ten months. Indurated chancre of the frenum at 24, followed by the appearance of a roseola and mucous patches on the pharynx and tongue. Mercurial pills administered, which cause secondary accidents to disappear. Nevertheless the disease reappeared again, and again a number of pills were administered. No treatment was given for two years. Afterwards a palmar psoriasis developed which disappeared under mercurial treatment. The patient took regularly every year, for one month, potassium iodide, in doses of 3 grams daily. No symptoms for twelve years. Then, at the upper portion of the right supramaxillary bone there appeared a tumor which grew rapidly before it was diagnosed as luetic. This tumor disappeared under potassium iodide, 4 grams daily. In March, 1900, Desnos saw the patient for the first time, at which time he complained of vague discomfort and pain limited to the perineal region. Also there was mild pain at the meatus on urination. Catheterization showed the urethra clear. The median lobe of the prostate was painful and an exploratory bougie was followed by bloody urination. On rectal examination the prostate was enlarged and slightly protruding, with large nodulations and slight pain to pressure. The vesicles were normal. Urine clear, but contained some short filaments. A diagnosis of simple prostatitis was made and prostatic massage instituted. After six massages the symptoms were aggravated and discontinued. After two months without treatment the same symptoms were observed, but with a much more abundant discharge. Instillations of picric acid into the prostatic urethra caused a rapid diminution of the prostatic discharge and enlargement. This was in the month of May, and a long time afterward Desnos learned that it was at this time that the patient took potassium iodide in 3 gram doses daily. Seven years elapsed, with no genitourinary symptoms, but during this time a bony tumor appeared again on the malar process and receded under treatment. Eighteen months later the prostatic symptoms returned, similar to those first seen by Desnos. The prostate was enlarged and poorly defined,

with marked protuberances. The median lobe was very painful and there was an abundant serous discharge. There were the same uneasy sensations, sometimes even intensely painful in the groins, but no pain on urination. Again prostatic massage and instillations of picric acid were employed, but produced no effect. Six weeks later the symptoms were more marked. A month elapsed without treatment; the gland increased in size and became adherent to the rectum. At this time the patient consulted a surgeon, the condition was diagnosed as cancer of the prostate and operation advised. The patient hesitated, sought other advice, and a diagnosis of syphilis of the prostate was made. Potassium iodide was administered, 6-8 gram doses daily, and little by little the symptoms disappeared, and five weeks later the prostate was normal.

CASE 2.—A man of 40, who at the age of 25 had suffered from a severe attack of syphilis, which had been treated by mercury inunctions. In January, 1910, he presented symptoms of a posterior urethritis and intermittent mucopurulent discharge, which was quite severe. This discharge was almost completely free from bacteria. Upon rectal examination the prostate was found enlarged, more so than those of ordinary chronic prostatitis. The lobes were enlarged, hard, without any well-defined borders. There was no discharge upon massage. Urination was slightly painful, the urine being cloudy in the first glass and clear in the second. There was pain in the perineal region, with intermittent shooting pains in the urethra to the meatus. Defecation was painful. Urethrovesical treatment was followed by scarcely any diminution of the symptoms. After a rest of several weeks the patient returned with the same symptoms slightly increased. The prostate was more enlarged and on the right less mobile, appearing adherent to the rectal mucosa. This peculiarity caused a diagnosis of syphilis, and potassium iodide in 4 and 6 gram doses daily was administered. Fifteen days later a diminution of the gland was marked. Gastric intolerance caused suspension of the potassium iodide for ten days, but one month later the prostate had regained its normal size and condition and all symptoms had disappeared.

In each of Desnos' cases there was a definite history of syphilis, and a considerably enlarged prostate returned to normal under the administration of potassium iodide. This seems to be sufficient evidence upon which to base a diagnosis of syphilis of the prostate, so these two cases are accepted as such.

OBSERVATION XII, JUNGANO,¹⁹ 1910

Jungano is quoted by Desnos as reporting a case in which symptoms of distress in the perineum, with considerable enlargement of the prostate, were relieved in twenty days under potassium iodide.

Reference to this case can not be found, and as the evidence is very meagre it is not accepted as one of syphilis of the prostate.

OBSERVATION XIII, COOK,²⁰ 1912

On May 4th, 1912, R. P., aged 38, presented himself to Cook's Clinic with the following history: gonorrhea about fifteen years ago, several subsequent attacks, the last one in 1910, which was completely cured. Sore on penis about 9 years ago, which was diagnosed chancroid and was followed several weeks later by a rash, sore throat, and alopecia. Syphilis was diagnosed and treatment by mouth instituted, which was continued for three or four months, causing the disappearance of all symptoms. The patient was in good health until the spring of 1908, when an ulcer appeared on the left tibia, which healed after several months of internal treatment. Frequent and difficult urination began in January, 1912, accompanied by fullness in the perineum, which became painful upon defecation when constipated. Deep pain in the perineum after coitus, which had grown worse until priapism was very painful. A discharge appeared the latter part of April. The patient had lost 20 pounds in weight during the past five months. Upon examination a general glandular enlargement was observed, patellar and pupillary reflexes were diminished, pigmented scars over both tibiae, with a necrotic subperiosteal gumma on left tibia. The spleen was slightly enlarged. There was a slight, thin, sticky, brownish discharge from the urethra and a stricture of the anterior urethra. The prostate was so large that its size could not be determined, and of the consistency of a hard rubber ball, pressure causing pain and increasing the discharge. The rectal wall was movable and no indication of fixation. The urine showed by the Wolbarst 5-glass catheter test: first, fourth and fifth glasses contain shreds and are cloudy, the remaining glasses negative. The urine contained, upon microscopic examination, bacteria, pus, epithelial cells and red blood corpuscles. A diagnosis of syphilis and malignancy of the prostate was made. Mercurial inunctions and potassium iodide were instituted and on June 5 arsphenamine was administered intravenously. By June 23 the prostate was normal in size and the patient felt perfectly well.

The evidence in this case seems to be sufficient upon which to base a diagnosis of syphilis, and it is therefore accepted as such. This case is the first to be reported in American literature.

OBSERVATION XIV, RUSH,²¹ 1913

CASE 1.—F. P., a man of 66, was seen by Rush on October 22, 1911. He had contracted syphilis in 1869, since which time he had religiously taken treatment at intervals consisting of mercury and potassium iodide three months each year and Donovan's solution for three years. The patient complained of bloody urine and constant desire to urinate, which had existed since 1910, although these symptoms had been somewhat lessened by a dose of arsphenamine received in April, 1911. Examination, October 22, 1911, revealed a prostate apparently as large as a hen's egg, indurated and very sensitive to pressure on the right lobe. The urine was dark and contained mucus, blood and pus. The Wassermann reaction was faintly positive. From October 22, 1911, until October 22, 1912, the patient received six intravenous and one intramuscular injection of arsphenamine,

and 26 intravenous injections of neoarsphenamine, with a reduction in the size of the prostate to one-third of that when first examined, with complete abatement of all urinary symptoms.

While the possibility of syphilis of the prostate must be admitted in this case, the fact that the prostate did not return to normal after a year of treatment, leaves an element of doubt, so it is not accepted as one of prostatic syphilis in this study.

OBSERVATION XV, WRIGHT,²² 1914

In August, 1911, a man of 42 came to Wright, stating that he had had painful and frequent urination since the summer of 1908, which lasted from two or three days to two or three weeks. These attacks were treated by irrigations and the passing of a sound. They increased in frequency and severity until January, 1911, when he was forced to go to bed, where he remained for three months having his bladder washed daily. A cystoscopic examination was said to have revealed five ulcers in the patient's bladder, but upon suprapubic cystotomy no ulcers were found. Upon examination nothing abnormal was found in the chest and abdomen and the reflexes and pupils were normal. In the center of the suprapubic scar was a fistula out of which urine dribbled, so he was compelled to wear a gauze pad. He passed with great difficulty two ounces of cloudy foul smelling urine. Catheterization immediately afterwards resulted in the finding of ten ounces of residual urine. The urine was loaded with pus and contained many bacteria, but no tubercle bacilli. Rectal examination revealed the prostate two or three times the normal size, the right lobe being somewhat larger than the left. The surface was uneven, but not nodular. It felt firm and hard, and at the same time gave a sense of elasticity and was very painful. At this time a history of a sore on the penis seventeen years before was obtained. This was diagnosed as syphilis, and he was ordered by his physician to Hot Springs. By the time he arrived there, the sore had entirely healed and he was advised that his condition was not syphilitic and he returned home without treatment. At the time of examination the Wassermann test was positive. He was placed upon mercurial treatment, receiving 0.3 of a gram of mercury salicylate hypodermically on August 31. This caused acute mercurial poisoning, which kept him in bed four days, but when seen again on September 6, his pain had markedly diminished and the residual urine was reduced to seven ounces, although no change in the size of the prostate could be detected. Fifty grains of potassium iodide per day were then ordered, and mercury salicylate in 0.2 gram doses was administered every other day until September 20. At this time the patient insisted on going home. Wright states that he was again seen in September, 1912, one year after beginning treatment; that he had taken the mercurial treatment ordered by Wright and one mercurial course at Hot Springs in January, 1912. The patient considered himself well, although the fistula remained open and catheterization revealed three ounces of residual urine.

Although the possibility of syphilis of the prostate must be considered in this case, the fact that Wright does not state the condition of this gland at the time of the last examination seems that there is scarcely enough evidence to warrant a diagnosis of prostatic lues. It is therefore not accepted in this series.

OBSERVATION XVI, ULRICH,²³ 1915

On June 17, 1913, S. T., aged 44 years, was seen by Ulrich, complaining of difficulty and frequency of urination, which had begun 15 days previously. He urinated 8 to 10 times during the night and a like number of times during the day, the act being accompanied by considerable pain and burning. He gave a history of having had a chancre at the age of 20 which he treated himself. No history of further symptoms of syphilis. On examination there was a slight mucus discharge from the urethra which showed no gonococci. There was no stricture of the urethral canal, but there were 250 c.c. of residual urine in the bladder, which was highly colored, cloudy, and presented a slight ammoniacal odor. Rectal examination revealed the prostate enlarged, the left lobe so much so that it could not be reached with the finger. The consistency was elastic and there were no nodules and no pain on pressure. There was an ulcer on the left leg and the Wassermann was positive, so a diagnosis of syphilis was made. However, the patient refused antiluetic treatment, and irrigations with silver nitrate and the passage of sounds daily were begun. This treatment caused the urine to improve, but the frequency and difficulty of urination remained the same. Finally on July 4, 0.4 grams of neoarsphenamine was injected intravenously, and by July 8 urination was normal, the amount of residual urine was reduced to 4 c.c., and the prostate greatly decreased in size. As the patient considered himself well, he refused further treatment.

There seems to be no doubt that Ulrich was dealing with syphilis of the prostate, so his case is accepted in this study.

OBSERVATION XVII, RAVOGLI,²⁴ 1916

CASE 1.—A. S., age 32, had had several gonorrheal attacks, of which he had been cured. Two years previous to examination he had a syphilitic infection, for which he took mercurial treatment and one full dose of arsphenamine. He complained of painful and frequent urination which prevented him from sleeping and interfered with his work. Examination of the urine by the two glass test showed the first cloudy, with shreds and some mucopus. The second glass less cloudy, the last drop being expelled with pain and tenesmus. Rectal examination revealed the prostate slightly enlarged, with a few irregular nodules on its surface. Posterior urethral and bladder irrigations resulted in no relief. Urethroscopic examination showed two ulcerations the size of a lentil in the lumen of the prostatic urethra, which were touched with a 3 per cent solution of silver nitrate. The Wassermann was positive and the patient placed upon antiluetic

treatment. At the same time the ulcerations in the prostatic urethra were treated locally and in a short time healed up completely. The urine returned clear, the frequency diminished, and the patient returned to his work.

CASE 2.—P. N., age 45, had suffered from syphilis for over 15 years, but with no symptoms for a long time. One of his children had a periosteal gumma of the right arm, which yielded to mixed treatment. The patient came to be treated on account of an unbearable pain deep in the perineum and rectum, together with tenesmus of the bladder and rectum. He complained of frequent urination, with pain, and with no relief after urinating. The urinary stream was small, difficult to start, and ending in drops. A sound could not be introduced on account of pain. Rectal examination revealed the prostate swollen and bulging like a ball, painful to the touch, somewhat softer in the middle. Under general anesthesia the perineum was opened, the prostate isolated, the capsule incised and bloody grumous purulent matter removed. The surface was cleaned with a dull curette and packed with iodoform gauze. In a short time recovery was perfect. The Wassermann proved slightly positive and antiluetic treatment with gray oil and potassium iodide was instituted. At the time of the report the patient was working every day and had never had any further urinary disturbances.

In the first of Ravogli's cases the evidence does not seem to be sufficient to justify the diagnosis of syphilis of the prostate, since no mention is made of the condition of the gland at the close of the treatment.

In the second case, although the patient gave a definite history of syphilis, and the findings at the operation were suggestive of gumma, the improvement of the symptoms might have resulted from the operation alone, independent of the antisyphilitic treatment.

OBSERVATION XVIII, PORTILLO,²⁵ 1917

The patient, age not stated, presented himself with an orchitis and diurnal and nocturnal pollakiuria and giving a history of chancre and mucous patches. The testicular lesions were recognized as bilateral syphilitic sarcocoele. The urethra was normal, but rectal examination revealed the right lobe of the prostate greatly enlarged, firm and insensitive. A diagnosis of sclerous syphilis of the prostate was made and eleven months of vigorous antisyphilitic treatment resulted in recovery.

It was impossible to secure the original article in this case, and although the evidence as given in the abstract seems rather meagre, it is nevertheless accepted as one of syphilis of the prostate, upon the assumption that the statement that complete recovery followed antisyphilitic treatment means that the prostate returned to normal.

OBSERVATION XIX, WARTHIN,²⁶ 1918

Warthin's observation was made postmortem on a young man with early so-called tertiary syphilis, clinically latent. Other clinical data and the gross pathology are not given. Histologically diffuse plasma-cell infiltration occurred throughout the stroma of the organ, and not around the gland spaces as in chronic gonorrhea. The infiltrations were perivascular, interstitial and not periglandular or subepithelial. Fibroblastic and angioblastic proliferation were prominent, and numerous giant cells occurred in the larger infiltrations, giving them the character of miliary gummata without caseation. Groups of spirochetes were found in these.

This is the only case of syphilis of the prostate, with the exception of Power's¹⁶ which is not accepted, in which the histologic picture is given.

OBSERVATION XX, AUTHOR'S CASE

A man of 39 came under my observation Nov. 22, 1916, complaining of vague, indefinite pains in the arms, legs and back. He denied gonorrhea, but admitted a sore on the penis 14 or 15 years previously, which was followed by lesions of the mouth and throat, but no skin eruption. At that time he took some medicine by mouth for about one month. In October, 1914, he came to Hot Springs and received 8 inunctions of mercury. In August, 1916, a Wassermann test on his blood was one plus. Following this he took potassium iodide until the time I saw him. Upon examination there was found to be a general superficial adenitis and a slight exaggeration of the knee jerks. His blood Wassermann was one plus. Otherwise the examination was negative. From November 22 to December 11 the patient received 8 intravenous injections of 0.01 gram of mercury benzoate and 3 intravenous injections of 0.4 gram arsphenamine. At this time he returned home and I did not see him again until December 21, 1919, at which time he returned to Hot Springs, complaining of headache, backache and difficulty of urination which had lasted about three weeks. He stated that he had had no specific treatment since I saw him three years previously except two intravenous injections of arsphenamine in July, 1918, although he had come to Hot Springs in December, 1918, and finding that I was not here had merely taken a course of baths.

Examination showed a slight enlargement of the superficial lymph glands, and increased knee jerks. Rectal palpation revealed the right lobe of the prostate considerably enlarged, (about the size of a small, hen's egg,) slightly nodular and quite tender. The left lobe was apparently normal in size, although it was a little tender. Prostatic massage caused a slight, dark brown, mucoid discharge to appear at the meatus. Examination for gonococci was negative. The Wassermann by the classical method with cholesterinized antigen was one plus, and by the ice-box method and the Thompson raw serum method, three plus.

The patient was placed upon daily intramuscular injections of mercury benzoate, 0.02 gram and on the third day following 0.6 gram of neoarsphenamine

intravenously. In one week the difficulty of urination had diminished and the prostate had decreased considerably in size. From December 21, 1919, to February 4, 1920, he received almost daily intramuscular injections of mercury benzoate and neoarsphenamine at intervals of seven to ten days. The difficulty of urination had ceased and the prostate was apparently normal in size, with no tenderness.

In view of the definite history of syphilis, the lack of gonorrheal history, the positive Wassermann, and the result of specific therapy, there seems no doubt that this was a case of syphilis of the prostate.

DISCUSSION

INCIDENCE

Only 24 cases purporting to be syphilis of the prostate, including the present one, can be found in a very thorough search of the literature. Of these 24 cases, 12, or 50 per cent, are not accepted for various reasons as undoubted syphilis of this gland. Therefore we certainly are able to say that either prostatic syphilis is a most rare condition, or that it is seldom recognized. Of the 24 cases reported, 7 were in American literature, 6 in French, 5 in Russian, 2 in Spanish, and 1 each in English and Polish, and 2 are unknown, as neither the original articles nor the references can be found.

ETIOLOGY

Stage of the Disease.—Of the 12 cases of prostatic syphilis which are accepted as authentic, the length of time following syphilitic infection is stated in 7, and this varied from 3 months in Ricord's case to 29 years in the first of Desnos' cases, the average being a little over 15 years. In 3 cases the patient denied syphilis and in Warthin's case the statement is made that the patient was suffering with tertiary syphilis, although the length of time following infection is not mentioned.

Age.—The age of the patient is given in 10 cases and varied from 18 in Ricord's case to 62 in Kudintseff's case, the average being 40 years.

PATHOLOGY

The gross pathology of all the accepted cases, except Warthin's, in which the gross pathology is not mentioned, was one of enlargement, the size varying up to the size of an adult fist in Grosplik's

case and to so large that the size could not be determined, in Cook's and Ulrich's cases. Nodules are recorded in two of the cases and the consistency is stated as hard in most of the cases, but in some it is said to have been "elastic" or of the consistency of a "hard rubber ball."

In 5 of the cases, the enlargement was mainly on the right side, in one on the left side, while in the others it was apparently bilateral.

In only two of the cases are the postmortem findings recorded. Ricord stated that the prostate consisted of a vast ulcer, while Warthin gives only the histopathology of his case which has been fully recounted above.

CLINICAL HISTORY

The most frequent symptom of prostatic syphilis is pain, which is described as "slight" to "violent" and in some cases is independent of urination, but in most cases aggravated by this act. It is, as a rule, located in the perineum, but sometimes radiates to the legs and urethra. Pollakiuria is the next most frequent symptom, but in none of the cases was it very marked.

A slight urethral discharge is recorded in 3 of the cases and in several a discharge was produced upon prostatic massage.

In 5 of the cases pain on pressure is recorded, while in 3 it is stated that the prostate was not tender.

Other less frequently recorded symptoms are hematuria, feeling of foreign body in the rectum, painful defecation, painful coitus and more or less residual urine.

The Wassermann is recorded in only 2 of the cases and was positive in each.

As a rule the urine is more or less cloudy, containing pus, mucus, epithelial cells and sometimes red blood cells, although in Drobnik's case the urine was normal.

DIAGNOSIS

There is nothing pathognomonic either in the symptomatology or the findings by rectal palpation in syphilis of the prostate, so the diagnosis must be made by exclusion, the history, the presence or absence of other symptoms of syphilis, including the Wassermann, and the results of specific therapy.

The condition must be differentiated from simple hypertrophy, prostatic abscess, tuberculosis and malignant and nonmalignant tumors.

PROGNOSIS

The prognosis of syphilis of the prostate is good, as in all of the accepted cases, except Ricord's and Warthin's, which came to autopsy, the condition improved under specific therapy. In most of them the prostate became entirely normal and the symptoms disappeared.

TREATMENT

The treatment of syphilis of the prostate is the treatment of syphilis. To the administration of arsphenamine intravenously and mercury, preferably by intramuscular injection, should be added one of the iodides. Recently I have found the intravenous injection of sodium iodide most satisfactory in the treatment of gummatus conditions, and it is very much to be recommended where potassium iodide by mouth is not well tolerated.

Local treatment is of no avail.

SUMMARY AND CONCLUSIONS

1. Only 24 cases purporting to be syphilis of the prostate have been recorded in the literature, and of these only 12, or 50 per cent, are accepted as authentic.
2. Syphilis of the prostate is certainly a rare condition, or else it is frequently overlooked.
3. There is nothing pathognomonic, either in the symptomatology or the findings by rectal examination, so the diagnosis must rest on other evidence.
4. The prognosis of prostatic syphilis is good.
5. The treatment is specific.

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SYPHILIS IN PREGNANCY AND LABOR*

By EDWARD L. CORNELL, M.D., AND A. W. STILLIANS, M.D., CHICAGO, ILL.

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THERE is considerable difference in opinion relative to the prevalence of syphilis among pregnant women. Some authors mention as high as 16 per cent, others as low as 3 per cent and 4 per cent. This wide difference is due to the source of material. It is of much more interest to obtain some idea of the average prevalence of the disease in an average community. We are optimistic enough to think that syphilis is not nearly as prevalent as we are led to believe. In a recent article¹ we called attention to the value of the routine Wassermann reaction in pregnancy. We have recently started to test out cases coming to the clinic at the Stock Yards Branch of the Chicago Lying-In Hospital and Dispensary. This work has not advanced as far as we should like to draw definite conclusions, but it comes close to the findings which are found in private cases. The cases presented at this clinic are drawn from the residents of the Stock Yards district. The men are employed in various capacities in the yards. The material includes Poles, Lithuanians, Italians, Irish, Jews, Americans, and Negroes. In fact, it is a true melting pot. There has been no selection in the material. Every patient entering the clinic, who is pregnant, has a Wassermann taken. In the charity field, this work more nearly resembles private practice than that of most dispensaries. If the higher percentages mentioned above are accurate, most physicians are missing a number of syphilitics in practice. We are sure that the average practice yields no such percentage. In fact, the physician in the country field has a much lower percentage than his brother in the city. The higher percentages are reported from hospitals and like places where one expects to get complications. Falls and Moore² report 11.3 per cent; Commiskey,³ 8 per cent; Menten,⁴ 13.45 per cent; and Adair,⁵ 6.5 per cent, or an average of 9.81 per cent from four sources. Who among us believes that one woman in ten in private practice is syphilitic? If this is true, then most physicians are negligent in the treatment of their patients.

At the time of writing 69 cases have been tested. Of this num-

*From the Chicago Lying-In Hospital, Chicago, Ill.

ber two gave a strong positive and one a slight positive. All of the positives occurred in colored patients. This is a percentage of 4:34. In this series there were six colored patients. If these are taken out, we find 63 whites gave no positives, while 50 per cent of the colored patients were syphilitic.

CASE 1.—Mrs. E., age 18, married less than a year, came to the clinic in the eighth month of her pregnancy. She gave no history of any trouble. We were surprised to get the report of a positive Wassermann. The second examination showed nothing except a slight glandular enlargement. Her husband's blood was tested and it gave 100 per cent positive. She was delivered a couple weeks later of a 3-pound baby which lived only one hour. No autopsy was obtainable.

CASE 2.—Mrs. W., para ii, came to the clinic in her eighth month. She complained of a sore on the vulva and shortness of breath. The former had been present a few weeks. It was diagnosed as a chancre of the clitoris. The Wassermann reaction was strongly positive. Under mercurial rubs the chancre disappeared quickly. She was delivered six weeks after her first visit, of an apparently healthy baby. She has refused further treatment. At the time of writing the baby is four months old and gaining nicely.

CASE 3.—Mrs. D., para iii, with one miscarriage, gave no history of any trouble. Examination showed no signs of syphilis. Her abortion had been diagnosed as a placenta previa case. After the slight positive Wassermann report she was asked to return, at which time she acknowledged a previous infection with lues. She is now under treatment. The pregnancy has not terminated.

The number of abortions occurring in this series is interesting:

	PARITY	LIVE CHILDREN	ABORTION OR STILLBIRTH	REMARKS
H	3	1	2	
M	5	2	2	
S	7	5	2	
H	2	1	1	
T	2	1	1	
B	4	3	1	
R	9	8	1	
M	4	3	1	
H	2	1	1	
J	6	5	1	
F	12	8	4	{ 1 child paralysis 1 mentally defective 1 tuberculous
G	3	2	1	
A	8	6	2	
H	6	5	1	
V	3	2	1	
D	3	1	2	{ High B/P with therapeutic abor- tions for last pregnancy.
F	9	6	3	
M	4	3	1	
	92	63	29	

Eighteen out of the 69 cases gave a history of abortion or stillbirth aside from one case which was syphilitic. This is a percentage of 26. Of the three syphilitics, one had aborted. Why this large number of abortions is seen is difficult to state. From the table above, it is noted that one-third of all pregnancies resulted in abortion or stillbirth. A few of these may possibly have syphilis in spite of a negative Wassermann. In the class of patients mentioned the hard life they lead and the lack of prenatal care may be a factor in producing abortions. However, we can not help but feel that many of the abortions could be traced to other sources such as bad teeth, infected tonsils, chronic appendicitis, low grade gall bladder disease, etc. In our former series 19.6 per cent of the private patients gave a history of abortion or stillbirth. The greater percentage among the hard working class evidently means poorer prenatal care, poorer hygienic surroundings, etc.

The effect of syphilis on the mother varies considerably. We know of no condition which is so deceptive. Often the patient has no objective or subjective symptoms which bespeak lues. We have been surprised more than once since instituting the routine Wassermann. They have no more distress from nausea and vomiting than usual. They have good appetites, gain weight, and progress many times as nicely as the nonsyphilitic. They often on the other hand, complain quite bitterly of headache. This can sometimes be relieved by pyramidon, etc., but many times it resists the usual measures employed. The glandular enlargements are not noted in many cases. Abortion is quite frequent unless the patient is placed under active treatment. The above remarks apply to the woman who is infected previous to the pregnancy.

The woman who is infected after pregnancy has started usually shows all the typical signs of syphilis. These are often more severe than those seen in the nonpregnant woman. The effect on the fetus depends largely on the time of inoculation. If infection takes place shortly after pregnancy begins, abortion or premature delivery and fetal death are the usual sequels. If later, after the fourth month, the fetus is usually carried to term and may be apparently healthy.

The Wassermann taken on the infant shortly after birth is not reliable, so it is difficult to state whether the child is syphilitic or not. As most of these infants are allowed to nurse the mother, it

is possible that they may be born healthy and contract the disease from the mother's milk. This is not highly probable. Most of these children give a positive Wassermann some time during their early childhood, at least after the second week.

The treatment of the syphilitic during pregnancy is more essential and more difficult than the treatment before or after pregnancy. Many physicians seem to hesitate to use mercury and arsphenamine. The important fact to recall is—the kidney in pregnancy is called upon to do more work and is therefore subject to rapid and severe damage. The use of mercury may cause kidney damage and result in a toxemia of pregnancy. It has been our practice to institute active treatment, using intramuscular injections of mercury daily for one month and also to give four increasing weekly doses of neoarsphenamine at the same time. If the disease is apparently very active, mercurial rubs are used the following month. The intramuscular course and neoarsphenamine are given every other month until delivery. The pregnant case usually receives at least two courses and occasionally four. After delivery the treatment is continued, increasing the interval until the Wassermann reaction is persistently negative. The case is followed for at least three years after the Wassermann becomes negative. The results of this procedure have been gratifying where the patient has been faithful in keeping her appointments. In most cases, however, the women fail in their part, for as soon as they feel better they think the treatment is unnecessary.

We have had no kidney lesions develop and no apparent bad effect from the active treatment. The teeth, which are so frequently affected by pregnancy, have not been a cause of any anxiety. The patient consults the dentist every other month. He is instructed to clean the mouth thoroughly at each visit and to repair temporarily any cavities which may develop. Milk of magnesia is used as a mouth wash at night and potassium chlorate in the morning.

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OCULAR SYPHILIS AND ITS TREATMENT*

WITH REPORT OF CASES

BY WILLIAM J. YOUNG, M.D., LOUISVILLE, KENTUCKY

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SYPHILIS of the eye may be divided into two stages; viz., (a) primary, (b) secondary and tertiary. The reason for combining the second and third stages is that the dividing line is so indefinite that in the majority of instances it is impossible to differentiate between the two with any degree of certainty.

Primary ocular lues is said to be very rare; but just why this should be true has always been a mystery to me. Inasmuch as it has been demonstrated by different authorities that patients with a primary luetic lesion may be reinfected by inoculation, i. e., by transfer of excretion from the lesion to other portions of the body, it seems strange that the eye is not the site of primary lues in a greater number of instances. The most common modes of infection are: (a) the practice of infected adults kissing children on the eyes, and (b) the now (fortunately) almost obsolete custom of attempting the removal of foreign bodies from the eye by licking the lids.

The primary lesion may appear on any portion of the exposed eye, the eyelid or the conjunctiva, and begins as a pimple. It may at first be mistaken for an hordeolum or chalazion. However, the rapidity with which it assumes a virulent form soon excludes these affections as well as malignancy; and the hardness and infiltration furnish means of differentiating it from local tuberculosis.

Differentiation between a primary lesion and a disintegrating gumma may be made by the fact that the primary sore is more acute and rapid in its manifestations, and a luetic history (inherited or acquired) may usually be obtained. In any lesion where primary lues is suspected, a dark-field examination should be made, and, of course, isolation of the *Spirochete pallidum* will place the question of diagnosis at rest. While good results may be secured with the India ink stain, I regard dark-field illumination as the

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most certain method of perfecting the diagnosis. However, the thickness of the slide and the stain used will oftentimes be the means of mistaking one of the other spirochetes for the pallidum; also in the dark-field the live germ may be found going through evolutionary changes, while it remains fixed in the stain. On the conjunctiva and eyelids we may have hyperemia, mucous patches, or gumma. The latter two lesions present much the same appearance as when found in other anatomic situations.

Stenosis of the nasal duct is another lesion which must be considered. Such strictures may be due to periostitis in the nasal duct or may extend from the nasal cavity by contiguity of structure. The obstruction caused by periostitis prevents the exit of fluid through the lumen of the duct, which then overflows upon the conjunctiva and trickles downward over the face. These duct strictures are usually relieved by dilatation and appropriate local treatment; but in some cases the lacrimal sac has to be removed. Among the rarer forms of ocular lues may be mentioned: acute and chronic periostitis and gumma within the orbit.

In the treatment of primary ocular lues the same rules should govern as in other primary lesions. Local treatment consists in a mild eye wash, such as saturated solution of boric acid, bichloride of mercury solution 1 to 10,000 or 1 to 20,000, etc. In gumma involving the eye the same rules also apply as in the treatment of gummatous lesions elsewhere.

In the treatment of ocular syphilis I have regarded the judicious use of atropine, to prevent adhesions between different parts of the eye during acute exacerbations, of paramount importance. The directions concerning the use of atropine should be under the control of the oculist. The ultimate result depends entirely upon this feature, since by the lack of atropine instillation damage may be inflicted which can never be remedied, i. e., adhesions may form which will not disappear under antisyphilitic treatment.

Ocular syphilis, being a manifestation of circulatory disease, and the eyes being of such importance to the human economy, one naturally reaches for the drug most potent in combating the symptoms. Arsphenamine is the most effective of all the agents known, and the one with which the control and improvement of symptoms may be most rapidly accomplished. It has been my custom to depend entirely upon the administration of arsphenamine, limiting

the number of injections only by the development of untoward symptoms, or the lack of improvement, in the latter case the oculist being the final judge. In this way I have given as many as twenty-three arsphenamine injections within twenty-two weeks, with most excellent results and without harm to the patient. In cases where I have given only six or eight injections of arsphenamine, and then resorted to mercury salicylate, in about fifty per cent of instances the eyes have shown a tendency to revert to their former condition after improvement, making the use of arsphenamine again necessary. This factor more than any other has shown me the importance of the continued use of arsphenamine.

The number of arsphenamine administrations necessary to reach syphilitic lesions within the orbit has been so uncertain that I have made it a rule to be governed entirely by the findings of the oculist. In the cases herein reported it will be noted that the number of injections ranged from six to twenty-three. Once the lesion is established as luetic, subsequent Wassermann examinations are of little importance except as an index to the treatment of the constitutional disease. Usually by the time chronic ocular symptoms have been made to subside, the blood stream will be free from spirochetes.

In chronic eye lesions of luetic origin it is always well to administer iodide of potassium in conjunction with arsphenamine. Mercury may be given for its general effect, but seldom have I seen it produce much change in the ocular symptoms. Moreover, just how much benefit may be expected from the use of iodide of potassium I have not accurately determined; but the good effect it may have on adhesions is to be considered as well as its direct action upon the luetic infection.

In reporting the following cases uninteresting and useless details in connection with family and personal history will be omitted, and for the sake of brevity, specific dates of treatment will likewise not be shown in the therapeutic survey. The dosage of arsphenamine and neoarsphenamine intravenously administered varied between 0.2 and 0.6 grams, hence specification of the quantity in each instance seems unnecessary. Mercury salicylate was given intramuscularly in doses ranging from one-half to two grains each. The Wassermann reaction test was made upon the blood only.

CASE 1.—M. A., female, aged eleven years, date of admission to the clinic

February 4, 1918. She had complained for a week of intense photophobia and pain. Her vision was greatly reduced, pupils contracted, and responded slowly to atropine, media cloudy, but no opacities of vitreus. Diagnosis: inherited syphilis with iritis and iridocyclitis. Wassermann four-plus.

Therapeutic Summary.—Between February 4 and September 3 there were administered twenty-three injections of arsphenamine. Three mercury inunctions were given during the first three months. No improvement in the eye lesions was noted until after the twelfth injection of arsphenamine. Between September 15, 1918, and February 19, 1919, the patient received fourteen injections of mercury salicylate. February 27 examination showed: vision O. D. 20/20, O. S. 20/20, fundus and media clear; in other words, normal vision in both eyes. The Wassermann was then negative, and the patient was given a rest from treatment for four weeks. Between April 9 and July 17 twelve injections of mercury salicylate were administered. The Wassermann remained negative.

Summary of Eye Findings.—March 8, 1918, pupils partially dilated; media still cloudy; no apparent improvement. May 10 eyes improving slowly; vision O. U. 20/100. August 27 media clearing; vision O. D. 20/70, O. S. 20/50. February 27 eyes normal; vision O. U. 20/20.

CASE 2.—E. B., female, aged six years, date of admission July 2, 1918. Diagnosis: inherited syphilis with bilateral interstitial keratitis. Examination: O. D. central corneal ulcer 2 mm. in diameter; light perception only. O. S. vision 20/70. Wassermann four-plus.

Therapeutic Summary.—Between July 2 and September 3 the patient was given eight injections of arsphenamine or neoarsphenamine. September 26, vision O. D. light perception, O. S. 20/50+. Between September 26, 1918, and February 27, 1919, fifteen injections of mercury salicylate were administered. Examination February 6 showed vision O. S. 20/100, i. e., the vision was beginning to weaken. A rest from treatment for four weeks beginning March 6 was then given. April 10, Wassermann still four-plus. April 24 $\frac{1}{2}$ grain mercury salicylate administered. Between April 24 and July 6 the patient received ten injections of arsphenamine or neoarsphenamine, and two doses of mercury salicylate,—June 30 and July 13. Examination July 6 showed: O. D. central macula 2 mm. in diameter, vision light perception, O. S. 20/20 or normal. Wassermann negative.

CASE 3.—S. B., female, aged forty years, admitted August 5, 1918. Diagnosis: left-sided iritis, probably syphilitic. Vision O. S. light perception only. Wassermann negative.

Therapeutic Summary.—Between August 9 and October 8 the patient was given seven doses of arsphenamine. Examination then showed: vision O. S. 20/50. Between October 21 and December 30, eleven injections of mercury salicylate were administered. Examination then showed: eye lesion greatly aggravated, vision O. S. 20/100. January 3, 1919, arsphenamine treatment resumed, but after two injections had been administered the patient left the city and thus passed from observation.

CASE 4.—A. F., female, aged twelve years, date of admission May 3, 1918. diagnosis: inherited syphilis with bilateral iritis. The patient had complained

for six months of photophobia; pupils reacted very slowly to atropine; vision O. U. 20|100. Wassermann four-plus.

Therapeutic Summary.—Between May 3 and July 2 the patient was given eight injections of arsphenamine. Examination July 10 showed: vision O. U. 20|50; pupils moderately dilated; no adhesions of iris. Between July 10 and November 27 nineteen injections of mercury salicylate were administered. The following notes appear on the chart during that period. September 26 patient complained of sore throat; chlorate of potassium mouth wash prescribed. October 16 "eyes beginning to go back;" vision O. U. 20|70; moderate circumcorneal injection. Arsphenamine treatment resumed, nine injections being given between January 21 and April 21, 1919, with decided improvement in vision. Between May 5 and July 8, 1919, the patient received six injections of mercury salicylate, and was then given a rest of two weeks because of sore mouth. Examination July 8 showed: no circumcorneal injection; vision O. D. 20|20, O. S. 20|30; no adhesions of iris. Wassermann negative.

CASE 5.—A. C., female, aged thirty-six, admitted June 24, 1918. Diagnosis: syphilis, right-sided interstitial keratitis. Right cornea opaque, vision limited to finger count at ten feet. Wassermann four-plus.

Therapeutic Summary.—Between July 9 and August 30 the patient was given eight injections of arsphenamine, when examination showed: cornea clearing; vision improved, 20|100+. Between September 16 and November 11 seven injections of mercury salicylate were administered. Examination then showed: cornea opaque, vision only 20|200. Between December 3, 1918, and February 4, 1919, seven doses of arsphenamine were administered. The patient was then given permission to return to her home for a week and did not return for further treatment.

CASE 6.—N. L., female, aged nine years, admitted July 30, 1918. Diagnosis: inherited syphilis with bilateral interstitial keratitis. Examination: O. D. some photophobia; keratitis mostly central; iritis present; vision 20|200. O. S., keratitis, no iritis, vision 20|100. Wassermann four-plus.

Therapeutic Summary.—Between July 30 and December 17 the patient was given twenty injections of arsphenamine or neoarsphenamine. Examination December 24 showed: O. D. adhesions of iris; tension increased. O. S. cornea clearing, vision 20|50. Between December 24, 1918, and April 7, 1919, fifteen injections of mercury salicylate were administered. Examination March 31 showed: cornea clearing, but adhesions of iris made outlook grave. April 21 vision O. D. 20|200, O. S. 20|70. Between May 15 and July 17 the patient was given seven doses of arsphenamine or neoarsphenamine and three doses of mercury salicylate. Vision July 17, O. D. 20|100, posterior synechia, tension slightly increased. Vision O. S. 20|40, cornea not entirely clear. Wassermann negative.

CASE 7.—E. R., female, aged thirty-two years, admitted September 12, 1918. Diagnosis: syphilis, acute left-sided iritis. The left eye was acutely inflamed; blepharospasm was present, but there were no adhesions; circumcorneal injection marked.

Therapeutic Summary.—Between September 17 and October 22 the patient was

given six injections of arsphenamine, when examination showed: circumcorneal injection slight, no adhesions, vision O. S. 20/20 (with correction). Between October 28, 1918, and February 4, 1919, fifteen injections of mercury salicylate were administered. The patient was then given a rest from treatment for four weeks. March 12 Wassermann negative. The circumcorneal injection was increased and there was some pain. Between March 17 and June 24 the patient received fifteen injections of mercury salicylate, and was then given a rest of five weeks. Examination June 24 showed: circumcorneal injection slight, tension normal, iritis not entirely relieved. Wassermann negative.

CASE 8.—M. W., female, aged twenty-five years, admitted October 7, 1918. Diagnosis: inherited syphilis with left-sided interstitial keratitis. Left cornea opaque and vision limited to counting fingers at five feet. Wassermann four-plus.

Therapeutic Summary.—Between October 11, 1918, and March 17, 1919, the patient was given fourteen injections of arsphenamine. The chart shows examination December 17, 1918, vision O. S. 20/200; March 24, vision O. S. 20/70 and cornea clearing. Between March 24 and July 16 thirteen injections of mercury salicylate were administered. Examination July 16 showed: vision O. S. 20/100, slight circumcorneal injection, tension normal,—eye unimproved since last examination. Wassermann negative.

CASE 9.—A. S., female, aged nineteen years, date of admission, October 7, 1918. Diagnosis: syphilis, right-sided iritis. There was an ulcer on right cornea 1 mm. in diameter, almost central; considerable sloughing and keratitis; marked circumcorneal injection and iritis. Wassermann four-plus.

Therapeutic Summary.—Between October 8 and December 17, the patient was given six injections of arsphenamine, when examination showed: base of ulcer clean, iritis slight, no pain, eye clearing. Between January 7 and March 29, 1919, ten injections of mercury salicylate were administered. Examination then showed: ulcer healing slowly, circumcorneal injection slight. Wassermann negative.

COMMENTARIES

In the work described I have used the arsenical preparations and mercury separately with the idea of determining their relative values in the treatment of ocular lues. Just what results administration of the two agents at the same time would produce I have no means of judging, but the tendency of visual acuity to become less under mercury alone is sufficiently constant to suggest that its use is superfluous in the treatment of ocular symptoms of luetic origin.

In Case 1 the improvement was practically *nil* until after twelve injections of arsphenamine had been given. From that time there was steady improvement with the end result of normal vision.

This case shows the necessity of intensive treatment in ocular lues, as well as the continuation of the treatment over a long period of time. The patient was never made ill, nor were any noticeable symptoms produced, by the administration of arsphenamine. The negative Wassermann was to be expected. The administration of mercury is being continued with the idea of obtaining a complete clinical cure.

Cases 2, 3, 4, 5, and 6 emphasize the point which I have endeavored to make clear, i.e., that the stopping of arsphenamine and relying upon mercury alone results in retrogression of the ocular symptoms.

Case 7 represents one of typical syphilitic iritis and is included merely for the purpose of illustration. The other cases require no special comment.

The fact that these patients have been followed during abnormal (war) times, and that I was unable to always secure accurate reports of the eye findings from oculists, will explain the seeming incompleteness of my records. In some of the cases I had to rely upon the subjective manifestations, and my general impressions are portrayed in the foregoing reports.

CONCLUSIONS

1. That primary ocular syphilis is rare, considering the various possibilities of infection.
2. That the use of atropine sulphate in ocular lues should be under the personal supervision of an oculist.
3. That arsphenamine is the most potent drug in the treatment of ocular syphilis, mercury alone having but little effect.
4. That the number of arsphenamine injections is limited only by untoward symptoms which may develop, or lack of improvement in the ocular lesions.
5. That, finally, the effect of mercury alone in ocular lues is uncertain and in a large percentage of cases will neither control nor improve the symptoms.

STANDARDIZATION IN THE TREATMENT OF SYPHILIS*

BY B. C. CORBUS, M.D., CHICAGO, ILL.

(Received for publication, February 1, 1920)

DURING recent years many attempts have been made to standardize the treatment of syphilis and as a result different sets of instructions have been issued to facilitate the care of patients thus afflicted.

My own special problem was in finding a method which not only answered the needs of a large dispensary where from sixty to eighty patients were seen daily, but at the same time one flexible enough to allow absolute individualization of the patient.

In submitting the following plan, which has been tried for ten months in the Illinois Social Hygiene Dispensary and in my own private practice, the author offers this as a suggestion only, as he believes the disease too capricious to be treated in an absolutely stereotyped method.

The classification that has here been adopted may seem arbitrary, but we believe it helpful in that it gives us a good basis from which to start our treatment. Cards 1 and 2 are of particular importance as we all appreciate that the curability of this disease is in direct proportion to the time of the presence of the primary lesion, and that the earlier a case comes under observation the sooner a cure can be effected. If this program is followed carefully, opportunity is given to completely cure the infection, not considering it cured, however, until the spinal fluid has been examined with negative results.

It has been the practice of the author to overtreat rather than undertreat patients during this period as errors in this direction prevent relapses. Throughout the whole series of records the neurosyphilitic is ever in mind. Early detection and treatment where there is spinal fluid involvement is the only prophylaxis against later subarachnoid implication. This plan offers a certain method for its early detection and a means of attacking the disease with a minimum of risk to the patient.

Since a recent editorial that appeared in the *Journal of the American Medical Association*, we have persistently refrained from spinal punctures during the active florid stage, lest we might draw the infection over into the spinal canal.

*From the Illinois Social Hygiene Dispensary, Chicago, Ill.

STANDARD SYPHILIS TECHNIQUE NUMBER 1									
Case No.		<div style="border: 1px solid black; display: inline-block; padding: 2px;"> EARLY PRIMARY SYPHILIS </div> <div style="display: inline-block; vertical-align: top; padding-left: 5px;"> <small>Spirochete Positive Blood Wassermann negative</small> </div>				Name			
BLOOD WASSERMANN: Date Finding SPIROCHAETA: Date Finding <small>When giving reaction state whether—none—mild—moderate—or severe. Regulate Arspenamine dose to weight of patient, 1 decigram for each 30 lbs. of body weight.</small>									
ARSPENAMINE ONCE WEEKLY FOR SIX WEEKS									
<div style="border: 1px solid black; padding: 2px;">Date</div> <div style="border: 1px solid black; padding: 2px;">Dose</div> <div style="border: 1px solid black; padding: 2px;">Reaction</div>		<div style="border: 1px solid black; padding: 2px;">Date</div> <div style="border: 1px solid black; padding: 2px;">Dose</div> <div style="border: 1px solid black; padding: 2px;">Reaction</div>		<div style="border: 1px solid black; padding: 2px;">Date</div> <div style="border: 1px solid black; padding: 2px;">Dose</div> <div style="border: 1px solid black; padding: 2px;">Reaction</div>		<div style="border: 1px solid black; padding: 2px;">Date</div> <div style="border: 1px solid black; padding: 2px;">Dose</div> <div style="border: 1px solid black; padding: 2px;">Reaction</div>		<div style="border: 1px solid black; padding: 2px;">Date</div> <div style="border: 1px solid black; padding: 2px;">Dose</div> <div style="border: 1px solid black; padding: 2px;">Reaction</div>	
1ST WEEK		2ND WEEK		3RD WEEK		4TH WEEK		5TH WEEK	
MERCURY RUBS FOR FOUR WEEKS—PATIENT SHOULD CALL WEEKLY FOR OBSERVATION					ARSPENAMINE INJECTIONS ONCE WEEKLY FOR 3 WEEKS				
<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>	
7TH WEEK		8TH WEEK		9TH WEEK		10TH WEEK		11TH WEEK	
MERCURY RUBS FOR 4 WEEKS					ARSPENAMINE INJECTIONS ONCE WEEKLY FOR 2 WEEKS				
<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>	
16TH WEEK		18TH WEEK		19TH WEEK		17TH WEEK		18TH WEEK	
MERCURY RUBS FOR 4 WEEKS					ONE INJECTION ARSPENAMINE				
<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>	
20TH WEEK		21ST WEEK		22ND WEEK		23RD WEEK		24TH WEEK	
BLOOD WASSERMANN: Date Finding SPINAL FLUID WASSERMANN: Date Finding <small>Make Blood Wassermann and Spinal Fluid Wassermann at end of course. If Blood Wassermann is positive treat as latent syphilis, [card 5]. If Spinal Fluid Wassermann is positive, treat as neuro-syphilis, [card 7]. If both are negative discontinue treatment. DISCHARGE TECHNIQUE: Negative Blood Wassermann every four months for one year after treatment has stopped.</small>									

This system was developed by Dr. H. C. Corbus, Chicago.

Bureau of Social Hygiene League, Chicago.

STANDARD SYPHILIS TECHNIQUE NUMBER 2.									
Case No.		<div style="border: 1px solid black; display: inline-block; padding: 2px;"> LATE PRIMARY SYPHILIS </div> <div style="display: inline-block; vertical-align: top; padding-left: 5px;"> <small>Spirochete Positive Blood Wassermann positive</small> </div>				Name			
BLOOD WASSERMANN: Date Finding <small>When giving reaction state whether—none—mild—moderate—or severe. Regulate Arspenamine dose to weight of patient, 1 decigram for each 30 lbs. of body weight.</small>									
ARSPENAMINE ONCE WEEKLY FOR 6 WEEKS									
<div style="border: 1px solid black; padding: 2px;">Date</div> <div style="border: 1px solid black; padding: 2px;">Dose</div> <div style="border: 1px solid black; padding: 2px;">Reaction</div>		<div style="border: 1px solid black; padding: 2px;">Date</div> <div style="border: 1px solid black; padding: 2px;">Dose</div> <div style="border: 1px solid black; padding: 2px;">Reaction</div>		<div style="border: 1px solid black; padding: 2px;">Date</div> <div style="border: 1px solid black; padding: 2px;">Dose</div> <div style="border: 1px solid black; padding: 2px;">Reaction</div>		<div style="border: 1px solid black; padding: 2px;">Date</div> <div style="border: 1px solid black; padding: 2px;">Dose</div> <div style="border: 1px solid black; padding: 2px;">Reaction</div>		<div style="border: 1px solid black; padding: 2px;">Date</div> <div style="border: 1px solid black; padding: 2px;">Dose</div> <div style="border: 1px solid black; padding: 2px;">Reaction</div>	
1ST WEEK		2ND WEEK		3RD WEEK		4TH WEEK		5TH WEEK	
FOUR WEEKS OF MERCURY—HAVE PATIENT CALL WEEKLY FOR OBSERVATION.					ARSPENAMINE ONCE WEEKLY FOR 4 WEEKS				
<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>	
7TH WEEK		8TH WEEK		9TH WEEK		10TH WEEK		11TH WEEK	
FOUR WEEKS OF MERCURY RUBS					ARSPENAMINE ONCE WEEKLY FOR 3 WEEKS				
<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>	
15TH WEEK		16TH WEEK		17TH WEEK		18TH WEEK		19TH WEEK	
FOUR WEEKS OF MERCURY RUBS					ARSPENAMINE ONCE WEEKLY FOR 2 WEEKS				
<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>	
22ND WEEK		23RD WEEK		24TH WEEK		25TH WEEK		26TH WEEK	
FOUR WEEKS OF MERCURY RUBS					ONE INJECTION ARSPENAMINE				
<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>		<div style="border: 1px solid black; padding: 2px;">Date</div>	
28TH WEEK		29TH WEEK		30TH WEEK		31ST WEEK		32ND WEEK	
BLOOD WASSERMANN: Date Finding SPINAL FLUID WASSERMANN: Date Finding <small>If Blood Wassermann is positive treat as latent syphilis (card 5). If Spinal Fluid Wassermann is positive treat as neuro-syphilis (card 7). If Blood Wassermann is Negative and Spinal Fluid is Negative apply discharge technique. DISCHARGE TECHNIQUE: Negative Blood Wassermann every four months for one year after treatment has stopped.</small>									

This system was developed by Dr. H. C. Corbus, Chicago.

Bureau of Social Hygiene League, Chicago.

Space should be left at the top of this card for spirochete examination the same as on Card No. 1.

STANDARD SYPHILIS TECHNIQUE NUMBER 3 — PAGE 1.

Case No. **EARLY** Blood Wassermann positive
SECONDARY Generalized Eruption. Name

BLOOD WASSERMANN Date Finding

When giving reaction state whether—none—mild—moderate—or severe. Regulate Arspenamine dose to weight of patient, 1 decigram for each 30 lbs. of body weight.

ARSPENAMINE INJECTIONS ONCE WEEKLY FOR 8 WEEKS

Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose
Reaction		Reaction		Reaction		Reaction		Reaction		Reaction		Reaction		Reaction	
1ST WEEK		2ND WEEK		3RD WEEK		4TH WEEK		5TH WEEK		6TH WEEK		7TH WEEK		8TH WEEK	

MERCURY RUBS FOR 8 WEEKS—HAVE PATIENT RETURN ONCE WEEKLY FOR OBSERVATION.

Date		Date		Date		Date		Date		Date		Date		Date	
9TH WEEK		10TH WEEK		11TH WEEK		12TH WEEK		13TH WEEK		14TH WEEK		15TH WEEK		16TH WEEK	

ARSPENAMINE INJECTIONS ONCE WEEKLY FOR 8 WEEKS

Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose
Reaction		Reaction		Reaction		Reaction		Reaction		Reaction		Reaction		Reaction	
17TH WEEK		18TH WEEK		19TH WEEK		20TH WEEK		21ST WEEK		22ND WEEK		23RD WEEK		24TH WEEK	

MERCURY RUBS FOR 8 WEEKS—HAVE PATIENT RETURN ONCE WEEKLY FOR OBSERVATION.

Date		Date		Date		Date		Date		Date		Date		Date	
25TH WEEK		26TH WEEK		27TH WEEK		28TH WEEK		29TH WEEK		30TH WEEK		31ST WEEK		32ND WEEK	

BLOOD WASSERMANN: Date Finding

If Blood Wassermann is positive treat as latent syphilis, [card 5]. If Blood Wassermann is negative continue treatment notwithstanding, repeating the above outline but using the other side of card or another sheet just like it.

This system was developed by Dr. B. C. Corbet, Chicago

Illinois Soc. of Hygiene League, Chicago

STANDARD SYPHILIS TECHNIQUE NUMBER 3 — PAGE 2.

Case No. **EARLY** Blood Wassermann positive
SECONDARY Generalized Eruption. Name

BLOOD WASSERMANN: Date Finding

When giving reaction state whether—none—mild—moderate—or severe. Regulate Arspenamine dose to weight of patient, 1 decigram for each 30 lbs. of body weight.

ARSPENAMINE INJECTIONS ONCE WEEKLY FOR 8 WEEKS

Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose
Reaction		Reaction		Reaction		Reaction		Reaction		Reaction		Reaction		Reaction	
1ST WEEK		2ND WEEK		3RD WEEK		4TH WEEK		5TH WEEK		6TH WEEK		7TH WEEK		8TH WEEK	

MERCURY RUBS FOR 8 WEEKS—HAVE PATIENT RETURN ONCE WEEKLY FOR OBSERVATION

Date		Date		Date		Date		Date		Date		Date		Date	
9TH WEEK		10TH WEEK		11TH WEEK		12TH WEEK		13TH WEEK		14TH WEEK		15TH WEEK		16TH WEEK	

ARSPENAMINE INJECTIONS ONCE WEEKLY FOR 8 WEEKS

Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose	Date	Dose
Reaction		Reaction		Reaction		Reaction		Reaction		Reaction		Reaction		Reaction	
17TH WEEK		18TH WEEK		19TH WEEK		20TH WEEK		21ST WEEK		22ND WEEK		23RD WEEK		24TH WEEK	

MERCURY RUBS FOR 8 WEEKS—HAVE PATIENT RETURN ONCE WEEKLY FOR OBSERVATION

Date		Date		Date		Date		Date		Date		Date		Date	
25TH WEEK		26TH WEEK		27TH WEEK		28TH WEEK		29TH WEEK		30TH WEEK		31ST WEEK		32ND WEEK	

BLOOD WASSERMANN: Date Finding SPINAL FLUID WASSERMANN: Date Finding

If Blood Wassermann is positive treat as latent syphilis, [card 5]. If Spinal Fluid Wassermann is positive, treat as neuro-syphilis, [card 1]. If Blood Wassermann is negative and Spinal Fluid Wassermann negative apply discharge technique.

DISCHARGE TECHNIQUE. Negative Blood Wassermann every four months for one year after treatment has stopped.

This system was developed by Dr. B. C. Corbet, Chicago

Illinois Soc. of Hygiene League, Chicago

STANDARD SYPHILIS TECHNIQUE NUMBER 4 — PAGE 1.											
Case No.		<div style="border: 1px solid black; display: inline-block; padding: 2px;"> LATE SECONDARY </div>		Blood Wassermann positive; Spinal Fluid Wassermann negative		Name					
BLOOD WASSERMANN: Date Finding SPINAL FLUID WASSERMANN: Date Finding <small>When giving reaction state whether—none—mild—moderate—or severe. Regulate Arspenamine dose to weight of Patient, 1 decigram for each 30 lbs. of body weight.</small>											
MERCURY RUBS FOR 4 WEEKS—HAVE PATIENT COME ONCE WEEKLY FOR OBSERVATION.											
1st WEEK Date <input style="width: 50px;" type="text"/>		2nd WEEK Date <input style="width: 50px;" type="text"/>		3rd WEEK Date <input style="width: 50px;" type="text"/>		4th WEEK Date <input style="width: 50px;" type="text"/>					
ARSPENAMINE INJECTIONS ONCE WEEKLY FOR 8 WEEKS											
Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>	
5th WEEK		6th WEEK		7th WEEK		8th WEEK		9th WEEK		10th WEEK	
MERCURY RUBS FOR FOUR WEEKS											
Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>					
13th WEEK		14th WEEK		15th WEEK		16th WEEK					
ARSPENAMINE INJECTIONS ONCE WEEKLY FOR EIGHT WEEKS											
Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>	
17th WEEK		18th WEEK		19th WEEK		20th WEEK		21st WEEK		22nd WEEK	
MERCURY RUBS FOR 8 WEEKS—HAVE PATIENT RETURN ONCE WEEKLY FOR OBSERVATION.											
Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>	
25th WEEK		26th WEEK		27th WEEK		28th WEEK		29th WEEK		30th WEEK	
31st WEEK		32nd WEEK									
BLOOD WASSERMANN: Date Finding SPINAL FLUID WASSERMANN: Date Finding <small>If, at the end of this course, Blood Wassermann is still positive and Spinal Fluid Wassermann negative, repeat this course from beginning. In that case use a fresh card of the same number as, e. g., card 4, page 1. If Spinal Fluid Wassermann is positive (test as neuro-syphilis [card 7]). If, however, Blood Wassermann is negative and Spinal Fluid Wassermann negative, repeat the above course substituting potassium iodide for the course of mercury rubs. In that case use form on the back of this sheet [card 4 page 2]. Then apply discharge technique. DISCHARGE TECHNIQUE—Negative Blood Wassermann every four months for one year after treatment has stopped.</small>											

This system was developed by Mr. B. C. Corbus, Chicago

Illinois Social Hygiene League, Chicago

STANDARD SYPHILIS TECHNIQUE NUMBER 4 — PAGE 2.											
		<div style="border: 1px solid black; display: inline-block; padding: 2px;"> LATE SECONDARY </div>		Blood Wassermann positive; Spinal Fluid Wassermann negative							
BLOOD WASSERMANN: Date Finding <small>When giving reaction state whether—none—mild—moderate—or severe. Regulate Arspenamine dose to weight of Patient, 1 decigram for each 30 lbs. of body weight.</small>											
POTASSIUM IODIDE FOR 4 WEEKS—50 GRAINS DAILY—PATIENT SHOULD CALL ONCE WEEKLY FOR OBSERVATION.											
1st WEEK Date <input style="width: 50px;" type="text"/>		2nd WEEK Date <input style="width: 50px;" type="text"/>		3rd WEEK Date <input style="width: 50px;" type="text"/>		4th WEEK Date <input style="width: 50px;" type="text"/>					
ARSPENAMINE INJECTIONS ONCE WEEKLY FOR 8 WEEKS											
Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>	
5th WEEK		6th WEEK		7th WEEK		8th WEEK		9th WEEK		10th WEEK	
11th WEEK		12th WEEK									
POTASSIUM IODIDE FOR 4 WEEKS—50 GRAINS DAILY—PATIENT SHOULD CALL ONCE WEEKLY FOR OBSERVATION.											
Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>					
13th WEEK		14th WEEK		15th WEEK		16th WEEK					
ARSPENAMINE INJECTIONS ONCE WEEKLY FOR EIGHT WEEKS											
Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/> Dose <input style="width: 50px;" type="text"/> Reaction <input style="width: 50px;" type="text"/>	
17th WEEK		18th WEEK		19th WEEK		20th WEEK		21st WEEK		22nd WEEK	
23rd WEEK		24th WEEK									
MERCURY RUBS FOR 8 WEEKS—HAVE PATIENT RETURN ONCE WEEKLY FOR OBSERVATION.											
Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>		Date <input style="width: 50px;" type="text"/>	
25th WEEK		26th WEEK		27th WEEK		28th WEEK		29th WEEK		30th WEEK	
31st WEEK		32nd WEEK									
If, after this course, Blood Wassermann is negative, repeat above course, substituting mercury rubs for the course of potassium iodide. In that case use a fresh sheet, card 4, page 1. Then apply discharge technique. If, however, Blood Wassermann is still positive and Spinal Fluid Wassermann negative, treat as Latent Syphilis using card 5.											

This system was developed by Dr. B. C. Corbus, Chicago

Illinois Social Hygiene League, Chicago

STANDARD SYPHILIS TECHNIQUE NUMBER 5 — PAGE 1.													
Case No. _____										<div style="border: 1px solid black; display: inline-block; padding: 2px;"> LATENT SYPHILIS </div> Un cured cases without symptoms except positive Blood Wassermann; Spinal Fluid Wassermann negative.		Name _____	
BLOOD WASSERMANN: Date _____ Finding _____										SPINAL FLUID WASSERMANN: Date _____ Finding _____			
If Spinal Fluid Wassermann is positive case should be treated as Neuro-syphilis. When giving reaction state whether—none—mild—moderate—or severe. Regulate Arspenamine dose to weight of Patient. 1 decagram for each 20 lbs. of body weight.													
POTASSIUM IODIDE FOR 4 WEEKS—50 GRAINS DAILY—PATIENT SHOULD CALL ONCE WEEKLY FOR OBSERVATION													
1st WEEK		2nd WEEK		3rd WEEK		4th WEEK							
Date _____		Date _____		Date _____		Date _____		Date _____		Date _____			
Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____			
ARSPHENAMINE INJECTIONS ONCE WEEKLY FOR 8 WEEKS													
5th WEEK		6th WEEK		7th WEEK		8th WEEK		9th WEEK		10th WEEK			
Date _____		Date _____		Date _____		Date _____		Date _____		Date _____			
Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____			
POTASSIUM IODIDE FOR 4 WEEKS—50 GRAINS DAILY—PATIENT SHOULD CALL ONCE WEEKLY FOR OBSERVATION													
11th WEEK		12th WEEK		13th WEEK		14th WEEK		15th WEEK		16th WEEK			
Date _____		Date _____		Date _____		Date _____		Date _____		Date _____			
Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____			
ARSPHENAMINE INJECTIONS ONCE WEEKLY FOR EIGHT WEEKS													
17th WEEK		18th WEEK		19th WEEK		20th WEEK		21st WEEK		22nd WEEK			
Date _____		Date _____		Date _____		Date _____		Date _____		Date _____			
Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____			
MERCURY RUBS FOR 8 WEEKS—HAVE PATIENT RETURN ONCE WEEKLY FOR OBSERVATION													
23rd WEEK		24th WEEK		25th WEEK		26th WEEK		27th WEEK		28th WEEK			
Date _____		Date _____		Date _____		Date _____		Date _____		Date _____			
Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____			
BLOOD WASSERMANN: Date _____ Finding _____ If Blood Wassermann is positive repeat above course from beginning. In that case use form on back of this sheet. If Blood Wassermann is negative repeat above course subcutaneous in every rub for the course of potassium iodide, then apply discharge technique. In that case use same form and correct with pen DISCHARGE TECHNIQUE. Negative Blood Wassermann every four months for one year after treatment has stopped.													

This system was developed by Dr. B. C. Carlow, Chicago

Chicago Sanitarium Hygiene League, Chicago

STANDARD SYPHILIS TECHNIQUE NUMBER 5 — PAGE 2.													
Case No. _____										<div style="border: 1px solid black; display: inline-block; padding: 2px;"> LATENT SYPHILIS </div> Un cured cases without symptoms except positive Blood Wassermann; Spinal Fluid Wassermann negative.		Name _____	
BLOOD WASSERMANN: Date _____ Finding _____										SPINAL FLUID WASSERMANN: Date _____ Finding _____			
If Spinal Fluid Wassermann is positive case should be treated as Neuro-syphilis. When giving reaction state whether—none—mild—moderate—or severe. Regulate Arspenamine dose to weight of Patient. 1 decagram for each 20 lbs. of body weight.													
POTASSIUM IODIDE FOR 4 WEEKS—50 GRAINS DAILY—PATIENT SHOULD CALL ONCE WEEKLY FOR OBSERVATION													
1st WEEK		2nd WEEK		3rd WEEK		4th WEEK							
Date _____		Date _____		Date _____		Date _____		Date _____		Date _____			
Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____			
ARSPHENAMINE INJECTIONS ONCE WEEKLY FOR 8 WEEKS													
5th WEEK		6th WEEK		7th WEEK		8th WEEK		9th WEEK		10th WEEK			
Date _____		Date _____		Date _____		Date _____		Date _____		Date _____			
Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____			
POTASSIUM IODIDE FOR 4 WEEKS—50 GRAINS DAILY—PATIENT SHOULD CALL ONCE WEEKLY FOR OBSERVATION													
11th WEEK		12th WEEK		13th WEEK		14th WEEK		15th WEEK		16th WEEK			
Date _____		Date _____		Date _____		Date _____		Date _____		Date _____			
Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____			
ARSPHENAMINE INJECTIONS ONCE WEEKLY FOR EIGHT WEEKS													
17th WEEK		18th WEEK		19th WEEK		20th WEEK		21st WEEK		22nd WEEK			
Date _____		Date _____		Date _____		Date _____		Date _____		Date _____			
Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____			
MERCURY RUBS FOR 8 WEEKS—HAVE PATIENT RETURN ONCE WEEKLY FOR OBSERVATION													
23rd WEEK		24th WEEK		25th WEEK		26th WEEK		27th WEEK		28th WEEK			
Date _____		Date _____		Date _____		Date _____		Date _____		Date _____			
Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____		Reaction _____			
BLOOD WASSERMANN: Date _____ Finding _____ If Blood Wassermann is now negative, repeat above course, substituting mercury rubs for the course of potassium iodide. In that case make your entries later making necessary corrections on a fresh card No. 5. Then apply discharge technique. If, however, Blood Wassermann is still positive, go back and treat from beginning DISCHARGE TECHNIQUE. — Negative Blood Wassermann every four months for one year after treatment has stopped.													

This system was developed by Dr. B. C. Carlow, Chicago

Chicago Sanitarium Hygiene League, Chicago

STANDARD SYPHILIS TECHNIQUE NUMBER 6—PAGE 1.											
Case No.		<div style="border: 1px solid black; padding: 2px; display: inline-block;"> TERTIARY SYPHILIS <small>Skin lesions Bone lesions Mucous membrane Vascular Syphilis Blood Wassermann positive Spinal Fluid Wassermann negative</small> </div>				Name					
BLOOD WASSERMANN: Date Finding SPINAL FLUID WASSERMANN: Date Finding <small>If Spinal Fluid is positive case should be treated as Neuro-syphilis. When giving reaction state whether—none—mild—moderate—or severe. Regulate Arsenamine dose to weight of patient, 1 decigram for each 30 lbs. of body weight.</small>											
POTASSIUM IODIDE FOR 4 WEEKS—50 GRAINS DAILY—PATIENT SHOULD CALL ONCE WEEKLY FOR OBSERVATION											
1ST WEEK		Date		Dose		2ND WEEK		Date		Dose	
3RD WEEK		Date		Dose		4TH WEEK		Date		Dose	
ARSPHENAMINE INJECTIONS ONCE WEEKLY FOR 8 WEEKS											
Date		Dose		Date		Dose		Date		Dose	
Reaction		Reaction		Reaction		Reaction		Reaction		Reaction	
8TH WEEK		8TH WEEK		8TH WEEK		8TH WEEK		8TH WEEK		8TH WEEK	
POTASSIUM IODIDE FOR 4 WEEKS—50 GRAINS DAILY—PATIENT SHOULD CALL ONCE WEEKLY FOR OBSERVATION.											
13TH WEEK		Date		Dose		14TH WEEK		Date		Dose	
15TH WEEK		Date		Dose		16TH WEEK		Date		Dose	
ARSPHENAMINE INJECTIONS ONCE WEEKLY FOR 8 WEEKS											
Date		Dose		Date		Dose		Date		Dose	
Reaction		Reaction		Reaction		Reaction		Reaction		Reaction	
17TH WEEK		18TH WEEK		19TH WEEK		20TH WEEK		21ST WEEK		22ND WEEK	
MERCURY RUBS FOR 8 WEEKS—HAVE PATIENT RETURN ONCE WEEKLY FOR OBSERVATION.											
Date		Dose		Date		Dose		Date		Dose	
23RD WEEK		24TH WEEK		25TH WEEK		26TH WEEK		27TH WEEK		28TH WEEK	
BLOOD WASSERMANN: Date Finding SPINAL FLUID WASSERMANN: Date Finding <small>If Blood Wassermann is positive repeat above course from beginning. In that case use form on back of this sheet. If Blood Wassermann is negative repeat above course substituting mercury rubs for the course of potassium iodide then apply discharge technique. DISCHARGE TECHNIQUE: Negative Blood Wassermann every four months for one year after treatment has stopped.</small>											

This system was developed by Dr. B. C. Corbus, Chicago. Illinois Social Hygiene League, Chicago.

STANDARD SYPHILIS TECHNIQUE NUMBER 6—PAGE 2.											
BLOOD WASSERMANN Date Finding		<div style="border: 1px solid black; padding: 2px; display: inline-block;"> TERTIARY SYPHILIS <small>Skin lesions Bone lesions Mucous membrane Vascular Syphilis Blood Wassermann positive Spinal Fluid Wassermann negative</small> </div>				<small>When giving reaction state whether—none—mild—moderate—or severe. Regulate Arsenamine dose to weight of patient, 1 decigram for each 30 lbs. of body weight.</small>					
POTASSIUM IODIDE FOR 4 WEEKS—50 GRAINS DAILY—PATIENT SHOULD CALL ONCE WEEKLY FOR OBSERVATION.											
1ST WEEK		Date		Dose		2ND WEEK		Date		Dose	
3RD WEEK		Date		Dose		4TH WEEK		Date		Dose	
ARSPHENAMINE INJECTIONS ONCE WEEKLY FOR 8 WEEKS											
Date		Dose		Date		Dose		Date		Dose	
Reaction		Reaction		Reaction		Reaction		Reaction		Reaction	
8TH WEEK		8TH WEEK		8TH WEEK		8TH WEEK		8TH WEEK		8TH WEEK	
POTASSIUM IODIDE FOR 4 WEEKS—50 GRAINS DAILY—PATIENT SHOULD CALL ONCE WEEKLY FOR OBSERVATION.											
13TH WEEK		Date		Dose		14TH WEEK		Date		Dose	
15TH WEEK		Date		Dose		16TH WEEK		Date		Dose	
ARSPHENAMINE INJECTIONS ONCE WEEKLY FOR 8 WEEKS											
Date		Dose		Date		Dose		Date		Dose	
Reaction		Reaction		Reaction		Reaction		Reaction		Reaction	
17TH WEEK		18TH WEEK		19TH WEEK		20TH WEEK		21ST WEEK		22ND WEEK	
MERCURY RUBS FOR 8 WEEKS—HAVE PATIENT RETURN ONCE WEEKLY FOR OBSERVATION											
Date		Dose		Date		Dose		Date		Dose	
23RD WEEK		24TH WEEK		25TH WEEK		26TH WEEK		27TH WEEK		28TH WEEK	
BLOOD WASSERMANN: Date Finding <small>If Blood Wassermann is positive repeat above course from beginning. If Blood Wassermann is negative repeat above course substituting mercury rubs for the course of potassium iodide then apply discharge technique. DISCHARGE TECHNIQUE: Negative Blood Wassermann every four months for one year after treatment has stopped.</small>											

This system was developed by Dr. B. C. Corbus, Chicago. Illinois Social Hygiene League, Chicago.

STANDARD SYPHILIS TECHNIQUE NUMBER 7 PAGE 1.

Case No. _____ **NEURO-SYPHILIS** Tabs
Paras
Cerebro-spinal _____ Name _____
Spinal Fluid Wassermann positive and Blood Wassermann either positive or negative

BLOOD WASSERMANN: Date _____ Finding _____ SPINAL FLUID WASSERMANN Date _____ Finding _____
When giving reaction state whether—none—mild—moderate—or severe. Regulate Arspenamine dose to weight of patient. 1 decigram for each 30 lbs. of body weight.

ARSPENAMINE INJECTIONS TWICE WEEKLY FOR FIVE DOSES

Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____
1ST WEEK		2ND WEEK		3RD WEEK

At end of this course make LUMBAR DRAINAGE: Amount Removed _____ PAYMENT TO HAVE ONE MONTHS REST FROM ALL TREATMENT AFTER CONCLUSION OF ARSPENAMINE INJECTIONS

MERCURY RUBS FOR TWELVE WEEKS—HAVE PATIENT RETURN ONCE WEEKLY FOR OBSERVATION

Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
4TH WEEK	5TH WEEK	6TH WEEK	7TH WEEK	8TH WEEK	9TH WEEK
Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
10TH WEEK	11TH WEEK	12TH WEEK	13TH WEEK	14TH WEEK	15TH WEEK

ARSPENAMINE INJECTIONS TWICE WEEKLY FOR FIVE DOSES.

Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____
10TH WEEK		17TH WEEK		18TH WEEK

At end of this course make LUMBAR DRAINAGE: Amount Removed _____ PAYMENT TO HAVE ONE MONTHS REST FROM ALL TREATMENT AFTER CONCLUSION OF ARSPENAMINE INJECTIONS

Repeat the entire course of above treatment until Spinal Fluid becomes negative. When this stage is reached repeat the above entire course for one year notwithstanding negative Blood and Spinal Fluid. Use form on back of this sheet for repetition.

DISCHARGE TECHNIQUE. Negative Blood and Spinal Fluid Wassermann every year for three years after treatment has stopped.

This system was developed by Dr. B. C. Corbitt, Chicago. (When Secret Hygiene League, Chicago.)

STANDARD SYPHILIS TECHNIQUE NUMBER 7—PAGE 2.

Case No. _____ **NEURO-SYPHILIS** Tabs
Paras
Cerebro-spinal _____ Name _____
Spinal Fluid Wassermann positive and Blood Wassermann either positive or negative

BLOOD WASSERMANN: Date _____ Finding _____ SPINAL FLUID WASSERMANN Date _____ Finding _____
When giving reaction state whether—none—mild—moderate—or severe. Regulate Arspenamine dose to weight of patient. 1 decigram for each 30 lbs. of body weight.

ARSPENAMINE INJECTIONS TWICE WEEKLY FOR FIVE DOSES

Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____
1ST WEEK		2ND WEEK		3RD WEEK

At end of this course make LUMBAR DRAINAGE: Amount Removed _____ PAYMENT TO HAVE ONE MONTHS REST FROM ALL TREATMENT AFTER CONCLUSION OF ARSPENAMINE INJECTIONS

MERCURY RUBS FOR TWELVE WEEKS—HAVE PATIENT RETURN ONCE WEEKLY FOR OBSERVATION

Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
4TH WEEK	5TH WEEK	6TH WEEK	7TH WEEK	8TH WEEK	9TH WEEK
Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
10TH WEEK	11TH WEEK	12TH WEEK	13TH WEEK	14TH WEEK	15TH WEEK

ARSPENAMINE INJECTIONS TWICE WEEKLY FOR FIVE DOSES

Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____	Date _____ Dose _____ Reaction _____
10TH WEEK		17TH WEEK		18TH WEEK

At end of this course make LUMBAR DRAINAGE: Amount Removed _____ PAYMENT TO HAVE ONE MONTHS REST FROM ALL TREATMENT AFTER CONCLUSION OF ARSPENAMINE INJECTIONS

Repeat the entire course of above treatment until Spinal Fluid Wassermann becomes negative. When this stage is reached repeat the above entire course for one year notwithstanding negative Blood and Spinal Fluid.

DISCHARGE TECHNIQUE. Negative Blood and Spinal Fluid Wassermann every year for three years after treatment has stopped.

This system was developed by Dr. B. C. Corbitt, Chicago. (When Secret Hygiene League, Chicago.)

Note to the Editor

December 11, 1919.

To the Editor:

In the October number of the American Journal of Syphilis, Wyndham B. Blanton describes the history of postmortem findings in four fatal results in patients treated with salvarsan. His full and elaborate report of the histories and the postmortems seem to point so clearly to the cause of the fatal results that we feel that attention should be directed to what seems to be the cause of these deaths.

In Case 1, 3.4 grams of salvarsan was given in 6 doses from February 28th to March 18th, that is, in 18 days.

In Case 2, 2.4 grams of salvarsan was given in 5 doses from March 8th to March 26th, 18 days.

Case 3 received 2.1 grams of salvarsan in 4 doses from March 15th to March 26th, 11 days.

Case 4 received 2.7 grams in 5 doses from March 11th to March 26th, 15 days.

These injections were all given intravenously, and, as the weight of the patient was not reported, we will assume they were ordinary men, at least were not abnormally large men.

The most outstanding fact in the report under consideration is the large doses administered and the short intervals between the injections. The postmortem findings also all show acute hemorrhagic encephalitis, which would be expected from toxic doses of salvarsan.

Taken in connection with the large doses, the short intervals, the clinical history of the toxic symptoms and the postmortem findings, we feel sure that the main point in the whole subject is that the doses of salvarsan were too large and given at too short intervals.

Our experience during the past nine years, in which time we have administered about 15,000 injections of salvarsan and neosalvarsan, has convinced us that excellent results may be obtained from doses less than half as large as those given by Dr. Blanton and at intervals of not less than six or seven days. We are also equally sure that such large and frequent doses are dangerous; in fact, we are not a little surprised that more of his patients did not manifest toxic symptoms if they were all given these large doses with such short intervals. There is nothing in the report which would lead one necessarily to the conclusion that the product he used was abnormally toxic; in fact, just the contrary is shown by the large amount tolerated by the patients before the fatal results occurred.

We feel that a definite warning should therefore be given against the administration of such large and frequent doses of salvarsan. We believe that our extensive use of this remedy and our experience with it justifies us in hoping our opinion may carry sufficient weight to prevent similar fatal results without jeopardizing the therapeutic results which would be expected.

We administer .2 to .4 gram doses of salvarsan with intervals of about one week until 8 or 10 such injections are given. The courses of treatment are repeated whenever serologic or clinical evidence indicates the necessity of further treatment; of course, supplementing the treatment with mercury, and with iodides as well, when indicated.

Although not relevant to the above subject we should like, nevertheless, to take this opportunity to refer to another subject which has been under discussion recently regarding pneumonia following injections of salvarsan in concentrated solutions.

Of the previously mentioned 15,000 injections of salvarsan, about 10,000 were given by the syringe method in an average dilution of 50 c.c. for each dose. In not a single instance have we seen pneumonia follow the injections. Naturally, therefore, and not without adequate reason, we believe such concentrations do not cause pneumonia.

Edgar G. Ballenger, M. D.,
Omar F. Elder, M.D., Atlanta, Ga.

Atlanta, Ga.

Raise in Subscription Price

With the January issue of The American Journal of Syphilis the subscription price will be raised to \$6.00. As a reason for this increase, we only need point to the fact that the cost of printing and paper, and the making of illustrations has increased from one hundred to three hundred per cent since the Journal started three years ago.

The publishers feel that the readers of this Journal prefer to pay an additional cost of one dollar a year rather than have the quality of the Journal lowered in any particular.

Erratum

On page 22 of the January, 1920, issue of the American Journal of Syphilis, in the article by Dr. José Luis Carrera, "A Pathologic Study of the Lungs in One Hundred and Fifty-Two Autopsy Cases of Syphilis," line 22, the word "vascular" should read "avascular."

Abstract of Current Syphilis Literature

It is the purpose of this JOURNAL to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Wm. H. Deaderick, Dugan-Stuart Bldg., Hot Springs, Arkansas.

WM. H. DEADERICK, M.D., EDITOR

THE INCIDENCE OF SYPHILIS AMONG WHITE AND COLORED TROOPS AS INDICATED BY AN ANALYTICAL STUDY OF THE WASSERMANN RESULTS IN OVER TEN THOUSAND TESTS.—William Levin, Parsons, Kansas. *Journal of Laboratory and Clinical Medicine*, 1919, vol. v, p. 93.

Wassermann tests made for a year at the U. S. Army Base Hospital, Fort Riley, Kansas, indicated the existence of a definite percentage of syphilis among the white and colored troops. Based on the double-plus reactions alone, there were 10.5 per cent syphilitics among the white and 18.3 per cent syphilitics among the colored soldiers. Considering the single-plus reactions in this series also diagnostic, the percentage of syphilitics was 13.8 for the white and 24.1 for the colored soldiers. Estimate is made that the same and probably higher percentage of syphilitics exists among the white and colored civilians of the ages 21 to 31.

SYPHILIS AND IMMUNITY.—C. Simon. *Le Bullétin Medicale*, 1919, vol. xxxiii, No. 41, p. 544.

There is no such thing as real immunity to syphilis. The peculiar condition of the organism in the course of syphilitic infection approaches on the contrary the state of allergy described by von Pirquet in tuberculosis. According to modern theories, which take into account the recent biologic disorders and especially the phenomena of immunity and anaphylaxis, the organism possesses a mixture of incomplete immunity and anaphylaxis, or rather sensitization. The existence of this sensitization is shown by the necessity for a period of incubation and by the successive development of the disease. Before the chancre can make its appearance, the treponema sensitizes the territory, probably through the secretion of its toxins. Although the treponema is known to pass into the blood from the fifth day on after the inoculation, it does not

give rise to pathologic reactions until later; indicating that the entire organism must first be sensitized. These states of immunity and sensitization develop together in the organism, and from their admixture, with predominance of either, originate the extremely variable phases seen in the evolution of syphilis. When the level, as it were, of sensitization is superior to that of the immunity, symptoms appear, their gravity increasing in proportion to the difference in levels. At the onset of the chancre, a relatively strong lesion originates because the immunity is still weak as compared to the sensitization. At the time of the secondary stage, the immunity is stronger than the sensitization during the latent phases, whereas it becomes lower, but in a weaker proportion during the outbreak of the lesions. The secondary symptoms are really superficial, this generalization being due to only a large number of treponemas in the circulating blood, namely, a state of septicemia. The tertiary stage is characterized by a progressive weakening of the immunity and of the sensitization, the latter remaining, however, at a decidedly higher level, hence production of severe deep lesions even with a very small number of germs. Finally immunity and sensitization disappear, and a new infection may occur. These reinfections behave like a new infection; they are clinically very rare, although perhaps less exceptional than is usually assumed to be the case.

NATURE OF LATENT MENINGITIS IN SYPHILIS.—A Sezary. *Paris Medical*, 1919, vol. ix, No. 40, p. 268.

The author emphasizes that no scientific proof has been advanced of the syphilitic nature of the latent meningeal inflammations which occur in syphilitics, meaning the direct determination of the meningitis by the treponema, which is merely probable but has never been demonstrated. On the basis of recent histomicrobiologic findings, the author propounds the theory, compatible with all known facts, that the treponema lodges primarily, not in the nervous centers, which it reaches through the general circulation. The meningitis would thus represent an ordinary reaction of the serosa in the vicinity of the foci of growth of the parasite, and undoubtedly also of the sclerotic and degenerated tissues. The process might be compared with the reaction of the peritoneum in the vicinity of infected or degenerated abdominal viscera. The meninges are known to be liable to become influenced when in contact with primary lesions of the nerve center, whether aseptic (cerebral softening, tumors, insular sclerosis) or microbic (*zona*, *lyssa*). Very recently it has been shown that in wounds of the brain, the intracranial suppuration may be accompanied by a meningeal syndrome with an aseptic purulent reaction of the cerebrospinal fluid. Briefly, the meningitis revealed by spinal puncture in syphilitics

seems to the authors to be a witness (instead of the cause) of the parenchymatous nervous lesions with which it is associated. As such, it is of importance for the early diagnosis of nervous luetic affections and for the direction of the treatment. It is not, however, the common basis of these nervous disturbances, and is not entitled to the importance attributed to it by certain therapeutic methods which aim at influencing it directly through the intraspinal route. Although this interpretation of latent syphilitic meningitis is still in part theoretical, the author now desires to bring it to the attention of syphilographers and neurologists.

SPIROCHETES AS RELATED TO PARALYTIC PROCESSES.—F. Jahnel. *Correspondenz-Blatt für Schweizer Aerzte*, 1919, vol. xlix, No. 33-34, p. 1277.

The demonstration of spirochetes in the brain of paralytic patients has led to a series of extremely important and interesting pathologic findings. Spirochetes have been discovered in only one-fourth to at most one-half of the cases (dark-field illumination) and are not any oftener demonstrated in cerebral puncture fluids. Their number is subject to great local and temporary changes in individual cases. Remissions in the course of paralysis are to be interpreted as intervals due to the liberation of antibodies. Two types of distribution of spirochetes can be distinguished: first, their localization in strictly circumscribed foci; second, their diffuse distribution. The seats of predilection are the anterior portions of the brain, especially the frontal pole gyrus rectus. It would not seem to be justified to insist upon the demonstration of spirochetes in all cases of paralysis, in view of their rarity in many brains, but their presence may be assumed in every paralytic brain. The paralytic seizures are acute exacerbations, anatomically represented by an enormous destruction of nervous tissue. At the same time, a very active and extensive proliferation of spirochetes takes place in the brain, more particularly in definite cortical territories. Death in a paralytic attack means not only death through cerebral lesions, but death due to the action of spirochetes. Paralytic seizures comprise, besides epileptiform and apoplectiform attacks, sudden more or less complete loss of consciousness, and other sudden psychic aggravations. In such cases, masses of spirochetes are formed, as in a congenitally syphilitic liver. No action of spirochetes on other organs enters into consideration in paralysis. No proof of any kind is available for the assumption of a toxic action. The spirochetes in these cases are rapidly destroyed. Salvarsan (arsenobenzol) treatment does not influence the findings. Febrile affections in paralytic patients may be followed by remissions as well as exacerbations; based on personal experience with a case of this kind, the author is enabled to state that even a severe suppuration

in the brain, as in purulent meningitis, exerts no influence upon the spirochetes and that the hope of controlling the paralysis by means of artificial production of leucocytes must be abandoned. The histologic change constitutes the terminal result of the gradually progressive pathologic process, while the spirochete picture reflects the condition prevailing at the instant of death. Hence the existing histologic findings must not be charged unconditionally to the spirochetes which happen to be present in that locality. The tissue reaction in paralysis is probably delayed, just as the secondary phenomena of lues are preceded about three weeks by an inundation of the blood with spirochetes. The two modes of spirochete distribution may merely represent different stages of the same process. Spirochetes have been demonstrated in the blood vessels of the brain and presumably penetrate the vascular walls as a result of their free motility. Their multiplication in the brain is suggested by the appearance of clusters of colonies. It still remains an open question why the spirochetes do not lodge in other organs of paralytic patients. They may persist for years in sclerotic scar tissue, as well as in pigmentations after healed skin eruptions; such remnants have a tendency toward excentric distribution, a similar regional migration of the virus probably occurring also in the paralytic brain. Spirochetes are found only in the gray matter, occasionally in very small foci of spherical form. In paralysis, the gray cortex constitutes a perennial and constantly renewed infectious focus, from which the parasites may enter the blood, but are carried back again by the blood into the nervous system. The variable distribution of the paralytic process in different cases is referable to the localization of the spirochetes, which varies in individual cases. Diffuse affections are accounted for by repeated disseminations through which each locality is repeatedly attacked by spirochetes in the course of the paralytic process.

STATISTICAL STUDY OF EXTRAGENITAL CHANCRES.—Horace Wray Porter, St. Louis. *Archives of Dermatology and Syphilology*, 1920, vol. xxxviii, p. 15.

This article was written merely for the purpose of adding to the statistics now existing on extragenital chancres and the general average is not claimed to be of value in a grand total. The author is satisfied in finding that the relative location of the lesions is in accord with all the literature on the subject.

SYPHILIS OF THE CIRCULATORY SYSTEM.—Ivy Mackenzie. *Glasgow Medical Journal*, 1919, vol. xcii, No. 5, p. 209.

Syphilis is the most important factor in inflammatory vascular degeneration, and may occur (1) as arteritis in the secondary stage

in the brain, usually in association with meningitis; (2) as phlebitis or periphlebitis and venous thrombosis in the secondary stage; (3) as gummatous degeneration of large arteries, more particularly of the aorta in the tertiary stage, (4) as gummatous phlebitis in the tertiary stage; and (5) as gummatous degeneration of the brain arteries in the tertiary stage. From the point of view of the clinician, the most important of these degenerations is syphilitic aortitis, which not infrequently involves the aortic valves and coronary arteries, and which is the most common cause of aortic aneurysm. There is considerable doubt as to the period intervening between infection and the onset of aortitis. Histologic examination of the walls of a syphilitic aneurysm shows in the majority of cases that the infection has spent itself or is in a quiescent state.

Concerning the clinical results of aortic disease, it carries in its train, or is associated in its development with, first, aneurysm; second, endocarditis; third, narrowing of the coronary arteries; and fourth, myocarditis. Syphilitic inflammation is the most common cause of aortic aneurysm as well as of aneurysms in other elastic arteries, which are of less frequent occurrence. Aortic endocarditis is a frequent sequel or accompaniment of syphilitic aortitis, and in these cases, there is not unusually a narrowing of the lumina of the coronary arteries. The cardiac muscle is the seat of syphilitic degeneration far more than is commonly recognized. Large gummata occur seldom, but syphilitic inflammatory infiltration and fibrosis can be easily detected by microscopic examination in a large proportion of cases in which aortitis and endocarditis are present. Syphilis of the large elastic branches of the aorta is much rarer than aortitis, and is practically invariably associated with that condition; syphilis of the large muscular arteries is rarer still. The smaller muscular and elastic arteries are involved in all the structural reactions of syphilis which are proliferative or gummatous in character. The arterioles and smaller arteries are usually affected in the neighborhood of gross syphilitic lesions. The cases microscopic examination shows the pathologic process in the basal arteries of the brain are, however, the vessels of moderate size which most frequently exhibit characteristic changes. In recent arteries to be confined to the adventitia. The intima is usually the seat of extensive proliferative changes. In the cerebral arteries of recent syphilitic infection, spirochetes have been demonstrated in the vessel walls. With special reference to syphilis of veins, the small venous vessels are involved in the vascular disturbances associated with recent brain syphilis. At the site of primary infection as well as along the route of the infection, the venules are changed and affected, also in the cutaneous lesions, more especially in the papular syphilides and late secondary lesions of the ulcerative type. It is of great importance to note that not a few of the so-called

varicose ulcers of the lower limb are syphilitic in origin, and yield readily to antisypilitic treatment when other measures have proved fruitless.

The occurrence of circulatory complications will usually be avoided by early and thorough treatment of the infection when it is recognized in the initial stages. The greatest precaution must be observed in the treatment of aortitis and its coronary and myocardial complications. Not only is syphilitic aortitis the most common complication of the aorta, but it is the lesion of acquired syphilis most commonly found in the postmortem room of the general hospital. In these cases the Wassermann reaction is positive as a rule.

SYPHILIS IN JOINTS OF MOROCCO NATIVES.—Lacapère and Ch. Laurent. *Paris Médical*, 1919, vol. ix, No. 38, p. 221.

Syphilis is extremely common among the natives of Morocco, at least 75 per cent being affected, and shows a special predilection for certain regions of the body, notably the joints. Among 979 examined cases, 112 specific articular lesions could be noted. In spite of the very large number of cutaneous syphilides seen every day, the percentage of joint localizations reached over 10 per cent as compared to the sum total of specific manifestations among natives. This frequency of articular localizations is the result of the missing or insufficient treatment of native syphilis. The conclusion is justified that articular syphilis is more common and more serious among Morocco natives than in France, as a consequence of neglect on the part of the Arabs, who pay no attention to painless lesions and become functionally powerless without giving their condition a thought. Joint localizations of tertiary syphilis may be grouped under the headings of gummatous arthropathies, ankylosis-producing arthropathies, and syphilitic rheumatism. The articular ankyloses under the authors' observation were distributed as follows: Ankylosis of one elbow, eight cases, ankylosis of both elbows, four cases; ankylosis of the lower jaw, eight cases; ankylosis of one knee, four cases; ankylosis of both knees, two cases. Joint stiffening due to syphilitic rheumatism affects most frequently the elbow, but is not uncommonly localized in the shoulder and wrists. Surgical treatment, in the form of resection, is alone promising, but must, of course, be preceded by antisypilitic treatment to subdue the remnants of inflammation and guard against recurrences. The authors' observations include a restricted number of articular manifestations due to congenital syphilis, some identical with the articular lesions of acquired syphilis, others such as arthritis deformans, ankylosis of the spine, and malformation of the wrists, characteristic of congenital syphilis.

SECONDARY SYPHILIS OF THE UTERUS.—George Gellhorn, St. Louis, Mo. Surgery, Gynecology and Obstetrics, 1919, vol. xxix, p. 374.

In a syphilitic woman with a very recent infection, several ulcerated patches within the cervical canal constituted the first and only manifestations of secondary syphilis. The discovery of these lesions was made possible by an eversion of the cervical lips due to an old tear. A large number of the *Spirocheta pallida* could be demonstrated in the secretion of the patches. Secondary lesions of the cervix are quite rare. They have been found upon the outside of the vaginal portion, and this is the first case on record where the lesion was located within the cervical canal.

SYPHILIS OF THE LIVER.—Udo J. Wile, Ann Arbor, Michigan. Archives of Dermatology and Syphilology, 1920, vol. xxxviii, p. 139.

In the so-called secondary period, or in the first months of the infection, involvement of the liver is encountered occasionally in the form of jaundice, of which two distinct forms are noted: (1) mild icterus, and (2) grave icterus. Women seem to be somewhat more often affected with mild icterus than men. The jaundice is characterized by appearing rather suddenly and usually without symptoms. The absence of gastrointestinal symptoms is a valuable diagnostic aid in differentiating catarrhal jaundice, but as gastric symptoms not infrequently occur in early syphilis, they may also be present with syphilitic jaundice. Usually the icterus is a very transitory symptom, disappearing in a few weeks, and particularly under the influence of treatment. The brisk appearance of the jaundice, particularly coincident with the outbreak of the eruption; the absence of other causes, particularly the absence of gastrointestinal symptoms, and the prompt amelioration under specific treatment, are the important differentiating points. Simple catarrhal jaundice is the most difficult condition to exclude. The treatment is that for general syphilis. Grave icterus is far more rare than the benign form, but may supervene on apparently mild cases of jaundice. All of the cases of grave icterus which have been studied have contributed to a new cause for acute yellow atrophy. The author has observed one case of icterus gravis in which symptoms of acute yellow atrophy were present. This case, however, recovered, as have others in the literature when the diagnosis has been made sufficiently early and treatment instituted. The cases differ in no way in their symptomatology and course from those of acute yellow atrophy from other causes. By far the largest number of cases have occurred in women. The jaundice usually occurs at some time during the first year, frequently, as

in the mild jaundice, coincident with the exanthem. When unrecognized, cases run a fairly rapid course. The liver is enlarged, somewhat tender; then rapidly becomes smaller. There are marked gastrointestinal symptoms, and death usually ensues shortly after the onset of cerebral symptoms, which, as in other cases of acute yellow atrophy, indicate an early termination. The icterus at the beginning is usually mild, but becomes very intense with the progress of the disease. Crystals of leucin and trypsin indicating destruction of liver tissue are a uniform finding in the urine. When unrecognized, the cases are almost invariably fatal, the course being somewhat longer than in acute yellow atrophy from other causes. The late manifestations of syphilis of the liver are far more common than those of the earlier period. Diffuse interstitial hepatitis or syphilitic cirrhosis is by far the most common form of syphilitic hepatitis, although not the easiest to recognize clinically. It is not unlikely that many cases of supposedly hepatic cirrhosis from other causes are due to syphilis. In sixteen cases that have come under the author's observation during the last five years, alcohol has been a negligible factor. The onset is usually insidious, swelling of the abdomen due to ascites being the most prominent symptom. In many cases the ascites disappears and reappears with periods of well-being intervening. Later in the course of the disease there is swelling of the ankles and a general anasarous condition. In a case under the author's care at the present time the ascites has been so great as to require twenty-five tapings within a period of five months, the total amount of fluid removed being over 150 liters. Pain is a prominent symptom, being typical of liver pain, radiating to the shoulder. In some cases the pain may simulate that of cholelithiasis. The pain is probably explained in the largest number of cases by the associated perihepatitis. The urine is usually dark in the later stages; it is distinctly icteric and later contains albumin from the associated nephritis. Jaundice is probably an important differential point, as its occurrence in other forms of cirrhosis is far more common than in the syphilitic form. Vomiting, hematemesis and hemorrhage from the bowel, associated with varicosities of the gastrointestinal system, are not infrequent. The stools as a rule are not clay colored. Occasionally they are mixed with blood and pus from associated ulcers of the rectum or colon secondary to amyloid change. Enlargement of the spleen is one of the earliest and most constant findings of syphilitic interstitial cirrhosis. It is usually caused by chronic passive congestion or is associated with amyloid change. In practically all cases under the author's observation it has been a uniform finding. The increase in size is great and the consistency of the spleen is firm. If the diagnosis of amyloid spleen can be made it is extremely helpful in establishing the cirrhosis as

syphilitic in origin. Cachexia and great loss of weight occur sooner or later. An unusual syndrome of interstitial hepatitis is that simulating Banti's disease. The course of the disease is essentially chronic. In not a few cases, however, pneumonia, fatal hemorrhage and rapid emaciation bring about a rapid exodus. In the absence of other syphilitic findings, the differential diagnosis is extremely difficult. If other syphilitic symptoms are present, the small size of the liver, the absence of jaundice and the absence of gastrointestinal symptoms are strongly suggestive of syphilis. In cases in which the surface of the liver is markedly irregular, it is sometimes difficult to differentiate carcinoma. Ascites may be present in both carcinoma and syphilis and thus complicate the diagnosis. Cachexia is present in both. Rapid increase in size of the individual nodes on the surface of the liver more particularly indicates carcinoma. It must be said, however, that in many cases the differential diagnosis can only be made after a long period of observation. Before the present day of laboratory aid in the diagnosis of syphilis, the differential was far more difficult. A positive Wassermann test, of course, with due consideration to its limitations, and the occasional occurrence of syphilis and carcinoma together, furnishes one of the most valuable aids in the differential diagnosis. The absence of jaundice, the appearance of ascites late, the relative small size of the liver, serve to differentiate it from other forms of cirrhosis. The prognosis is bad, being much worse in this form than in other forms of syphilitic liver disease. The treatment is that of general syphilis. Next to interstitial hepatitis, the gummatous form is the most frequent type of syphilis of the liver. The gummas occur either in the form of miliary nodules or oftener, as larger tumors of the surface which by their absorption result in distortion and changes in the configuration of the organ. Pain occurs almost uniformly and is an extremely confusing symptom inasmuch as it is frequently identical with the pain of cholelithiasis and cholecystitis. It is typically hepatic pain with radiation to the right shoulder, occasionally sharp and paroxysmal in character, at other times simulating the pain of cholecystitis. In other cases the pain may be that of high abdominal tumor, being in the left hypochondrium and not radiating to the shoulder. In still other cases actual pain is not present, but patients complain of a feeling of pressure and weight. Jaundice may or may not be present. It is less common probably than pain, and when present is never an intense icterus. Usually it is of short duration. The occurrence of ascites in this form of liver disease is not so frequent as in the interstitial form. Fever occurs commonly in all types of liver disease and is therefore not infrequently found with gummas. There is nothing characteristic about the course of the temperature. Enlargement of the spleen is fairly common. Gastric

digestion is delayed. There may be hemorrhages from the bowel and stomach. The symptomatology of hepatic gumma is varied and is modified by the occurrence of syphilis in the neighboring viscera, and by such complications as nephritis, peritonitis and splenic enlargement. The most prominent and least variable symptom is the nodular enlargement of the liver. The course varies from months to years, resulting occasionally in spontaneous cure, in other cases in satisfactory cure under specific treatment; in still others in progressive cachexia and death from complications or from exhaustion. Recurrences may occur occasionally. In typical cases the diagnosis is not difficult. The palpation of the discrete rounded nodules on the surface of the liver, the other associated syphilitic findings and the positive complement-fixation test render the diagnosis relatively easy. Obscure cases, however, are frequently encountered in which the diagnosis is more difficult. It is particularly necessary to differentiate carcinoma of the liver. In this condition the more rapid increase in the size of the nodules during a short period of observation constitutes an important differential diagnostic point. Ascites and jaundice are perhaps more common in carcinoma; enlargement of the spleen is a more common finding in gummas. The prognosis varies according to the time at which the diagnosis is made. In early cases in which a diagnosis has been promptly made and specific therapy instituted, the prognosis may be said to be good, the lesions and the symptoms yielding readily to specific therapy. In the later cases in which cachexia has occurred, or in which there are amyloid changes, or in which extensive distention and distortion of the liver has occurred, particularly in those cases in which ascites has been a prominent feature for a long time, the prognosis is bad. The treatment is that of general syphilis.

SYPHILIS OF THE CARDIOVASCULAR SYSTEM.—G. Harlan Wells, Philadelphia. *Hahnemannian Monthly*, 1919, vol. liv, p. 624.

The data are based upon a clinical study of one hundred cases of cardiovascular syphilis that have come under the observation of the author in private and hospital practice. The average age of onset of cardiac symptoms was thirty-seven years. Seventy per cent of the cases gave a positive history of chancre. Thirty per cent denied any knowledge of chancre. Thirty per cent of the cases with history of chancre denied having had a skin rash or other secondary symptoms. The Wassermann test was positive in 100 per cent of the cases giving a history of a chancre. The Wassermann test was positive in 75 per cent of the cases that denied having had the chancre. Five per cent of the cases that clinically appeared to be the result of syphilitic aortitis failed to give a history of chancre

or a positive Wassermann. The shortest period from the appearance of the chancre to the development of cardiovascular symptoms was four years, and the longest period was twenty-eight years. The average time that elapsed from the appearance of the primary lesion until the case came under observation with cardiac symptoms was fifteen and a half years. The average time from the appearance of the chancre until the development of the cardiac symptoms was as follows: Pain in or about the region of the heart, 70 per cent. Dyspnea, 25 per cent. Diarrhea and digestive disturbances, 5 per cent. In the larger proportion of cases the date of onset of the cardiovascular disturbance was announced by the development of pain in or about the heart, dyspnea, palpitation, and frequently accompanied by a vertigo, and occasionally by a swelling of the feet. The character of the pain varied greatly but in the majority of cases the patient described the pain as being paroxysmal, but recurring at frequent intervals. A large proportion of the cases stated that the pain ran down the left arm, and a few described it as radiating to the shoulder. The pain occurred at some time or other in about 90 per cent of the cases. Dyspnea, as above stated, was the initial symptom in 25 per cent of the cases and appeared sooner or later in 98 per cent. Disturbance of the rate of the heart was recorded in 60 per cent. The rate was at or about normal in 10 per cent. Not recorded, 30 per cent. The average systolic blood pressure was 140, and the average diastolic blood pressure was 90. Seventy-five per cent showed increase in the area of cardiac dullness. No murmurs were audible in 40 per cent of the cases. Systolic murmur, alone, occurred in 30 per cent, aortic murmur in 25 per cent. Both aortic and systolic murmurs were audible in 5 per cent. It is probable that the percentage of double murmurs would be much greater than this if the cases were kept under observation for any length of time. Clinically, the most common symptom of syphilis of the heart and aorta is pain in or about the precordial region. This pain may be of sharp, shooting character, coming on at irregular intervals or may be dull and constant, aggravated by exertion. It is frequently stated that the pain in these cases is the result of sclerosis of the cardiac arteries and, while this statement is correct in a large portion of cases, it must be remembered that very severe pain may occur without any cardiac sclerosis whatever, as the result of degenerative changes in the heart muscle. In other cases, dilatation of the aorta and aneurysm with pressure may give rise to the pain. Dyspnea is a very constant, and frequently a characteristic symptom of syphilitic aortitis and myocarditis. Dyspnea, associated with this lesion, is characteristically of a frequently recurring character and is aggravated by slight exertion, and accompanied by a sense of deficient lung ventilation and inability to hold the breath at will. Weakness on physical or mental exertion, vertigo, and persistent

headaches, especially after mental effort, are other symptoms very commonly present. Physical signs are enlargement of the area of cardiac dullness which is usually present and is frequently very marked. Mitral regurgitation is common.

A CLINICAL PATHOLOGICAL STUDY OF AN UNUSUAL SYPHILITIC MANIFESTATION RESEMBLING JUXTA-ARTICULAR NODULES.—Herman Goodman, New York and William Jackson Young, Louisville, Ky. *American Journal of Medical Sciences*, 1920, vol. clix, p. 231.

A case of multiple and symmetrical gummata of the tendons is described which clinically closely resembles the tumors of juxta-articular nodules. The microscopic picture is very different, however, and hence the two conditions can not be confused. Unfortunately the authors were not able to observe the effect of antisypilitic treatment, but the suggestive history, positive Wassermann, and histology of one of the lesions puts the diagnosis of multiple syphilitic gummata of the tendons on a sound basis.

SYPHILITIC FIBROSIS OF PENIS (KELOID TYPE) IN A NEGRO; REPORT OF A CASE.—H. W. E. Walther, New Orleans. *New Orleans Medical and Surgical Journal*, 1920, vol. lxxii, p. 481.

Not the least interesting phase of the case was the differential diagnosis. The patient, at first, gave a misleading history of his condition. The author therefore attempted to diagnose by elimination. Elephantiasis, fibrosis, malignancy, tuberculosis, syphilis, and adenoma were all considered. However, the physical examination, study of the blood, the usual microscopical aids and a truthful history finally obtained from the patient permitted a diagnosis.

AORTITIS SYPHILITICA.—C. F. Hoover, Cleveland. *Journal of the American Medical Association*, 1920, vol. lxxiv, p. 226.

Percussion for aortic dullness to the right of the sternum should be done by the direct palpating method. If this method of percussing is employed, the examiner will find that the projection of the aorta on the anterior thoracic wall, as determined by percussion, will not be inferior to the projection of the silhouette of the aorta as seen by the roentgen ray, and under some conditions the information gained by percussion is more dependable. An increase in pulsatory expansion of the aorta during systole may be detected by palpating bimannually. Further evidence of enlargement of the ascending arch of the aorta is accentuation of the aortic second sound and the palpable diastolic impact perceptible at the second interspace to the right of the sternum. A palpable diastolic im-

pact over the second interspace to the right of the sternum is perceptible in the adult only when there is increased accessibility of the arch. Should the aorta lose its elasticity, to compensate for the short duration of the pulse we should have a maximum systolic rise both in volume and in pressure, and a consequent lowering of the minimum diastolic pressure; but this modification of the pulse occurs only when the elasticity of the entire aorta is impaired, or at least when a very large portion of the aorta is involved. A murmur during the cardiac systole is audible over the second interspace at the right of the sternum when the ascending arch of the aorta is dilated, and also when there is stenosis of the orifice without dilatation of the arch of the aorta. Should the ascending arch and the root of the aorta be sclerosed, but the valves remain competent, then there would be present the physical conditions essential for the production of a systolic murmur and a tympanitic aortic second sound; but the intensity of the sound and the palpability of the diastolic impact and the systolic impulse would all depend on the dilatation of the arch of the aorta beyond its origin. Diagnosis of disease of the coronary arteries is not made by direct examination, but inferentially, by the history one is able to procure from the patient. In the early stages of syphilitic disease of the coronary artery, when therapeutic measures are of value, the diagnosis of coronary disease is based on a patient's history and his ability to exercise and not on any direct physical findings. Syphilitic mediastinitis is a common accompaniment of syphilitic disease of the aortic wall. Substernal pain, inclusion of the laryngeal nerve, paroxysmal tachypnea, and pain on swallowing have all been observed. The only direct physical sign of syphilitic mediastinitis, quite apart from functional disturbances, is the location of a friction sound audible at the second interspace to the right of the sternum. The Wassermann reaction, *Spirochæta pallida*, and the roentgen ray have all served to confirm and illuminate the work of great clinicians, but bacteriology and pathology lagged many years behind the clinic in dealing cogently with syphilitic aortitis.

ORBITO-CRANIAL SYPHILIS.—Charlin. *Annales d'Oculistique*, 1919, vol. clvi, No. 4.

Tertiary syphilis of the orbit is rather common; it may be superficial, affecting the bones of the orbital circumference, or deep and retroocular, rarely involving the soft tissues of the orbit, almost invariably the bony walls. The localization of the lesions is responsible for the clinical appearance; the symptoms are not characteristic of a syphilitic origin. The diagnosis is suggested by the following symptoms: Intraorbital lesion: exophthalmos, with or without involvement of ocular nerves. Extraorbital lesions: no exophthalmos, but the orifices of the orbit are usually involved,

in the region of the optic canal, the optic nerve may be compressed; the ophthalmoscope shows nothing at the onset but slight congestion of the retinal veins; later on, the papilla becomes pale and discolored, due to degeneration of the optic trunk. The lesion may sometimes concern the two optic nerves simultaneously.

When the sphenoidal fissure is involved, multiple ocular paralyses or pareses are met with (paralytic strabismus, diplopia, limitation of movements of the eyeball, paralytic mydriasis) or anesthetics, hyperesthesias, ocular neuralgias, or trophic disturbances of the cornea; as well as palpebral edema, conjunctival chemosis congestion of ocular veins. When the sensory and motor nerves are simultaneously affected, a sensory-motor ophthalmoplegia follows; when a lesion of the optic nerve is superadded, the syndrome is designated as sensory-sensitive-motor ophthalmoplegia. The extension of the process to the sphenomaxillary fissure leads to sensory disturbances of the lower eyelid, the cheek and the gums (superior maxillary nerve). When the lesion progresses backwards, the picture of basal meningitis supervenes, with headache, sometimes vomiting, cerebrospinal lymphocytosis, signs of intracranial hypertension, and so forth. Briefly, the symptomatology is variegated and the localization can usually be recognized without difficulty. The author contributes ten instructive personal observations.

CONGENITAL ENDOCRINIC SYPHILIS AND THE PART PLAYED BY IT IN CERTAIN DYSTROPHIES AND DEGENERATIVE DISEASES OF INDIVIDUALS AND RACES.—R. Barthélemy. *Annales des Maladies Vénériennes*, 1919, vol. xiv, No. 10, p. 577.

In discussing congenital endocrinic syphilis, and the part played by it in certain dystrophies and degenerative diseases of individuals and races, the authors point out the possible existence of endocrine glandular debility of congenital syphilitic origin. Conditions of this kind are evidently referable to an invisible biopathologic invasion, or to the sooner or later manifested instability of metabolic equilibrium, caused by congenital syphilis and appearing on the slightest intercurrent provocation. This interpretation serves to explain the developmental errors and nutritional disturbances of all kinds, which are directly dependent upon the regulating trophic system and the pathogenesis of which has long remained obscure. The reason why congenital syphilis so frequently gives rise to partial or total dystrophies is because these dystrophies, aside from those which are due to the actual presence of the treponema (sequelae of meningitis, keratitis, etc.), are the direct result of an affection of the endocrine glands, which manifests itself by disturbances of bodily and intellectual growth or of the metabolic equilibrium. This condition is transmitted to the offspring with

the definitely acquired blemishes of the parent, which impair the development and nutrition of the descendants. The dystrophy thus becomes hereditary, and the race is impoverished. Nevertheless, however, the virulence of treponema and its transmission have ceased, the immunity of congenital syphilis has disappeared, and the dystrophic individual is exposed to the danger of a new infection.

THE EARLY DIAGNOSIS OF SYPHILIS.—E. B. Tauber, Cincinnati, Ohio. *Journal of the American Medical Association*, 1919, vol. lxxiii, p. 1661.

No single sign of improvement should be accepted as definite or final, and treatment should not be stopped at such indication. Only cessation of all-around symptoms is indicative, and that only if it continues through years. Arsphenamine therapy is necessary, since it controls infectivity and contagion. It yields quick results. Mercury is essential but as a splint to our arsenic therapy and as an aid to permanence in cure. Most syphilis is undertreated. Sledge-hammer blows are indicated. Overtreatment is to be preferred to undertreatment. It is better to be overconservative rather than optimistic in stating that a cure has been effected. Our modern therapy is still in too infantile a stage to justify anything but overconservatism.

THE DIAGNOSIS OF PRIMARY SYPHILIS BY CULTURE.—Fred W. Baeslack and William E. Keane, Detroit. *Journal of the American Medical Association*, 1920, vol. lxxiv, p. 392.

In the course of study on the cultivation of *Spirocheta pallida*, it was found that this organism can be grown from human tissue directly, when small pieces of such tissue are planted on horse serum medium. This medium consists of normal horse serum, free from preservatives, diluted with sterile distilled water in the proportion of 3:1. The diluted serum is put into ordinary test tubes, which are closed with rubber stoppers, previously sterilized. The tubes are filled to within an inch of the top, stoppered, and heated to 60° C. for one hour in a water-bath. The following day the temperature is brought to 70° C. for one hour, and the next day the medium is heated at 70° C. until it takes on the consistency of syrup. The tubes are then stored in the refrigerator. The heating on the three successive days not only gives the medium a semisolid consistency, but also drives the air from the medium, so that it is under a partial vacuum. Whenever the location of the suspected sore permits, the tissue is removed by circumcision; otherwise a thin slice of tissue is removed with a razor from the edge of the lesion. The tissue is then planted, and is pushed into the

medium from one-half to two-thirds of the length of the tube. The tube, if taken from the refrigerator, should be warmed to body temperature before the implantation is made. If the lips of the tube are thoroughly heated so that the surface of the medium begins to boil, the air above the medium is sufficiently rarefied to permit replacing the rubber stopper without difficulty after inoculation. The inoculated tubes are incubated at 37° C. from three to five days, when a few drops of the medium near the tissue are removed with a pipet to a slide for dark-field examination.

THE PRESENT STATUS OF THE WASSERMANN REACTION.—L. C. Todd, Charlotte, N. C. *Southern Medical Journal*, 1919, vol. xii, p. 667.

Avoidable errors occur especially with careless technic, unclean glassware or improperly standardized reagents. The technician should have an accurate determination of the value of all his reagents and a complete control system whenever the test is set up, in order that he may never be in the dark regarding the action of any one of the constituents of the test. The only unknown quantity should be the patient's serum. It does not seem unfair to state that the Wassermann reaction is one of the most accurate of routine clinical laboratory tests performed today when properly controlled and performed carefully under sufficient standardization of reagents. Along with physical examination it is one of the greatest diagnostic aids. It may be adapted to show the influence of treatment. Greater uniformity of results will come with the adoption of a more nearly standard method.

THE LOSS OF COMPLEMENTING POWER IN GUINEA-PIG SERUM AT VARIOUS TEMPERATURES.—Joseph W. Bigger, Dublin, Ireland. *Journal of Pathology and Bacteriology*, 1919, vol. xxii, p. 323.

The methods described in this paper afford a satisfactory means of estimating decreases in the complementary powers of sera over considerable periods of time. Sterile guinea-pig serum retains its complementary power for a longer time than is generally conceded. The rate of loss of complement in such serum is more rapid at first than later. The higher the temperature the more rapid is the loss of complementary power. At temperature between 9° C. and 50° C. the rate of loss is regular, and the complement is destroyed in accordance with a definite mathematical expression, as is shown by the fact that the relationship between the strength of complement remaining (x) at a given time (t) from the commencement of the experiment, are expressed by the differential equation:

$$\frac{dx}{dt} \cdot \frac{1}{x^{n+1}} = K$$

TRAUMATIC HEMOLYSIS AND THE WASSERMANN REACTION.—George Manghill Olson, Minneapolis. *Journal of Laboratory and Clinical Medicine*, 1920, vol. v, p. 259.

In order to avoid traumatic hemolysis Olson advocates the following method in washing sheep's corpuscles: Two or three c.c. of sheep's blood are poured into 50 c.c. centrifuge tubes filled with 0.9 per cent cold salt solution. The tubes are centrifuged at moderate speed. The supernatant salt solution is removed. The tubes are again filled with salt solution. A small bit of cotton is wound around the tip of a wooden applicator. With this cotton tipped applicator the corpuscles are carefully removed from the bottom of the tube and gently stirred. Two washings are sufficient.

A COMPARATIVE STUDY OF THE WASSERMANN TEST AND THE HECHT-WEINBERG-GRADWOHL MODIFICATION.—A. J. Blaivas, Brooklyn, N. Y. *Journal of Laboratory and Clinical Medicine*, 1920, vol. v, p. 244.

The following results were obtained by Blaivas with 100 comparative tests, which were not selected cases, but those applying to the Brooklyn Diagnostic Institute for general diagnosis: (1) In 65 per cent of the sera the Wassermann and the Hecht-Weinberg-Gradwohl tests were either positives or negatives in both tests. (2) Nineteen per cent of the sera showed a positive or borderline in the Hecht-Weinberg-Gradwohl test and a one-plus or a borderline in the Wassermann reaction. (3) Seventeen per cent had no hemolytic index. (Of course in these cases the Hecht-Weinberg-Gradwohl test could not be employed.) (4) Five per cent showed a strong positive in the Hecht-Weinberg-Gradwohl test, and a negative in the Wassermann. (5) Five per cent showed a positive in Tubes 12 and 13 in the Hecht-Weinberg-Gradwohl test and negative in the Wassermann. (6) Four per cent showed a positive in Tube 13 in the Hecht-Weinberg-Gradwohl test and a negative in the Wassermann. (7) Two per cent showed very doubtful reactions. (8) The average hemolytic index was four, not including those sera that had no index at all. Blaivas' experiences with the Hecht-Weinberg-Gradwohl test, not only in this series reported, but also of former work, permit him to state that the Hecht-Weinberg-Gradwohl gives not only a faint inhibition of hemolysis, but sometimes a complete hemolysis in Tubes 11 and 12 and a complete or faint inhibition of hemolysis in Tube 13. It may also give a complete hemolysis in Tube 11 and a faint or complete inhibition in Tubes 12 and 13, and finally it may give a faint inhibition in Tubes 11, 12 and 13. Any of these reactions would be termed borderline reactions.

THE ICE BOX FIXATION METHOD IN THE PERFORMANCE OF THE WASSERMANN REACTION.—R. G. Owen and F. A. Martin, Detroit. *Journal of Laboratory and Clinical Medicine*, 1920, vol. v, p. 232.

Owen and Martin examined the sera of 1,113 patients, 500 of whom gave a definite history of lues or showed symptoms of a syphilitic nature, 500 without any history or symptoms of lues, and 113 classed as doubtful. Of the 500 cases of known syphilis with cholesterinized antigen incubated at 37.5° C. for one hour, 76.6 per cent were positive, 4.6 per cent doubtful, and 18.8 per cent negative. With plain alcoholic extract antigen incubated at 37.5° C. for one hour, 51.6 per cent were positive, 7 per cent doubtful, and 41.4 per cent negative. With plain alcoholic extract antigen incubated at ice box temperature, (7-10° C.) for four hours 70.6 per cent were positive, 3.2 per cent doubtful, and 26.2 per cent negative. Of the 500 clinically negative cases, cholesterinized antigen at 37.5° C. for one hour, gave 3.8 per cent positive, 6.6 per cent doubtful, and 89.6 per cent negative. Plain alcoholic extract antigen at 37.5° C. for one hour gave no positives, 1.4 per cent doubtful, and 98.6 per cent negative. Plain alcoholic extract antigen at ice box temperature, (7-10° C.) for four hours gave 0.2 per cent positive, 0.6 per cent doubtful and 99.2 per cent negative. Of the 113 cases classed as doubtful, cholesterinized antigen, 137.5° C. for one hour gave 39.8 per cent positive reactions, 11.5 per cent doubtful and 48.7 per cent negative. Plain alcoholic extract antigen, 137.5° C. for one hour gave 3.5 per cent positive, 7.9 per cent doubtful, with 88.5 per cent negative. Plain alcoholic extract antigen at ice box temperature, (7-10° C.) for four hours gave 7 per cent positive, 7 per cent doubtful and 86 per cent negative. Upon the above results Owen and Martin reached the following conclusions: (1) Simple alcoholic heart extracts give the most reliable Wassermann reactions, provided the first phase of the reaction is carried out at 7° C. to 10° C. (2) A period of four to six hours at this temperature gives the best results. Longer periods (twelve to eighteen hours) may give doubtful or weak-positive reactions. (3) We have found human heart extracts more dependable than beef or guinea pig heart preparations. (4) Cholesterinized antigens even when used in small quantities will give false-positive reactions in a considerable number of cases. Recent experiences which they had carried out and which they hope to report later, tend to show that a fifteen-hour fixation time gives a slightly higher percentage of positive results than is obtained with a four-hour fixation time. No better results have been obtained by extending the fixation time up to twenty-four hours.

THE WASSERMANN REACTION IN BREAST MILK.—D. A. Rojas. *La Semana Médica*, Buenos Aires, 1919, No. 30, p. 100.

The author's contribution is based upon 28 observations, including three repetitions. Eleven times, the reaction was determined in the milky secretion (colostrum) obtained in the course of the last month of pregnancy. Seventeen times the reaction was tested in the milk of puerperal women, which was invariably collected within five days following childbirth. All these reactions, with a single exception, were controlled by means of the blood serum reaction. The results obtained were as follows: Seven times the reaction was distinctly positive in both the blood and the milk, being more pronounced in the milk in three of the cases. In one instance, the reaction was positive in the blood, and negative in the milk; for this reason, the experiment was repeated, with the same outcome. Twice the reaction was positive in the blood and weakly positive or delayed in the milk. Four times the reaction was distinctly negative in both the blood and the milk. Six times the reaction was negative in the blood and weakly positive or delayed in the milk. In the tenth observation hemolysis was delayed in the blood and the reaction in the milk was positive. In two observations the reaction was weakly positive or the hemolysis was delayed (blood and milk). In one observation, hemolysis was delayed in the blood, and the reaction in the milk was negative. Finally, in one instance, in which the reaction in the milk was weakly positive, the blood was not examined.

As regards the time when the milk should be withdrawn in order to test the reaction, the author followed the indications of Thomsen in Germany (1910) who recommends never to take milk more than the fifth day after childbirth, because in the course of lactation the antibodies become so much diluted as to be no longer demonstrable. During the last two months of pregnancy it is possible to obtain up to 5 c.c. of secretion from each breast, a more than sufficient amount to carry out the investigation. The quantities of milk (serum) to be placed in each of the three test tubes differ from the amounts of blood serum used (0.2, 0.1, and 0.05 respectively), and the reaction is positive only when it appears in the second tube (0.1). Thomsen points out the possibility that the reaction in syphilitic women may be absent in the blood serum and exist in the milk, without offering an explanation of this fact, which was confirmed in six of the writer's observations, where the reaction was negative in the blood serum, while the hemolysis was retarded or weakly positive in the milk serum. The German observer also states that mercurial treatment apparently has no influence upon the reaction in the milk, as likewise in those women who do not suckle (dead child), and in those in whom the reaction was posi-

tive in the first days following childbirth, continuing to be so until the disappearance of the secretion. The author was unable to investigate these statements.

THE BORDET-WASSERMANN REACTION.—Jeanselme and M. Block. *Le Bulletin Médical*, 1919, vol. xxxiii, No. 41, p. 533.

The authors emphasize that in the interpretation of the findings in the Bordet-Wassermann reaction, certain facts must be kept in mind in order to guard against serious misconceptions. This special modification and capacity of syphilitic serum varies in degree according to the patients, according to the stages of the disease, according to the character and seat of the lesions. The technic of the reaction may yield doubtful and disputable results, on account of its complicated character, the fragility of the organic structures, and sometimes with weak degree of this special power of syphilitic secretions. Finally, the spontaneity of post-therapeutic development of the disease may cause the reaction to vary in the same patient. In a general way, energetic treatment, especially with arsenobenzol, is capable of influencing the reaction, changing it from positive to negative. Accordingly, the reaction may serve as a guide for the treatment, under observation of the following data: The earlier the treatment is instituted—the optimum period being the chancre before the first secondary symptoms—the more rapid is the reduction of the reaction, and the better the prospect of its remaining negative for a long time. As a routine procedure, a recent syphilitic should be treated with arsenobenzol until his blood reaction becomes negative. When this result has been accomplished, it is advisable to maintain it by means of mercurial medication. But a recurrence of the positive Bordet-Wassermann reaction, even in the absence of apparent symptoms, calls for the energetic resumption and continuation of arsenical treatment. The persistence of a positive blood reaction, in a recent syphilitic, in spite of energetic treatment, is usually suggestive of an encapsulated focus, especially a premature meningitis which should be ascertained by spinal puncture and treated accordingly.

OBSERVATIONS ON THE COLLOIDAL GOLD REACTION WITH CEREBROSPINAL FLUID.—Ellis Kellert, Albany, N. Y. *American Journal of the Medical Sciences*, 1920, vol. clix, p. 257.

The colloidal gold reaction is useful as an additional or confirmatory test. It is of greatest value in the syphilitic diseases of the central nervous system, especially tabes and paresis. The test may serve to differentiate between tuberculous and other forms of meningitis. The reaction is correct in approximately 80 per cent of cases. Cerebrospinal fluid contaminated with blood in small

quantity frequently gives reactions in the luetic zone. Positive results unconfirmed by other tests are of only slight value. The Wassermann reaction and the cytologic examination of the cerebrospinal fluid are of greater value than the colloidal gold test.

A STUDY OF THE COLLOIDAL GOLD REACTION AND ITS CLINICAL INTERPRETATION.—Margaret Warwick and Charles E. Nixon, Minneapolis. *Archives of Internal Medicine*, 1920, vol. xxv, p. 119.

The colloidal gold test is the most delicate of the routine spinal fluid reactions. With careful technic and proper attention to neutrality successful colloidal gold solutions are within the reach of every laboratory worker. It does not replace any other test but, on the other hand, is of independent value. It is of especial importance in the early diagnosis of neurosyphilis. The various curves are not specific but are of great diagnostic value in conjunction with other clinical and laboratory findings. A colloidal gold curve may be obtained with or without other positive findings after provocative treatment. The colloidal gold curve does not parallel clinical signs nor give definite evidence of improvement under treatment. Patients with no involvement of the central nervous system or who are nonsyphilitic give no colloidal gold curve. Clear-cut clinical cases of tabes dorsalis may show all the spinal fluid reactions negative both before and after treatment. A curve in zone III with a negative cell count and negative or faintly positive globulin is strongly suggestive of a brain or cord tumor or myelitis. Curves in zones I and II may be found in nonsyphilitic conditions, such as multiple sclerosis and brain abscess. A cell count above five is pathologic, but the cell count is of no value in indicating duration or severity of the process or improvement. This reaction should be included in every spinal fluid analysis and neurologic examination as well as in all cases of general syphilis.

LUMBAR PUNCTURE IN SYPHILIS.—P. Ravant. *La Presse Médicale*, 1919, No. 57, p. 573.

A complete examination of a syphilitic individual, with accurate establishment of his pathologic balance, must include the determination of the absence of a latent incipient meningitis, by means of lumbar puncture. The most favorable moment for this examination is as close as possible to the fourth year after the luetic infection. From this date on, the latent reactions gradually diminish in number, whereas on the contrary, the reactions accompanied by clinical signs increase. In practice, this examination is recommended at the beginning of the fourth year and about the tenth year. The first three years of syphilis represent a grave nervous change, although this is not yet manifested by any clinical sign.

Lumbar puncture may of course, be performed at any stage of syphilis; but in order to strike the greater frequency of latent reactions, it is but to keep within these two boundaries, thus increasing the prospects of discovering the latent stage of inflammation of the meningeal vessels, and thereby forestall the onset of the clinical symptoms. From the practical viewpoint, the author regards as follows the indications for examination of the cerebrospinal fluid in the course of syphilis:

1. When the luetic patient presents a clinical nervous disturbance, no matter at what stage of the disease, lumbar puncture will indicate if the lesion is accompanied by meningitis; more especially it will permit (preferably by the study of the leucocyte formula) the determination of the severity of the meningitis, and furnish a landmark for following its course.

2. When the luetic patient presents suspicious nervous disturbances, or phenomena of a psychic character, no matter at what stage of the disease, lumbar puncture may reveal the organic or the purely neuropathic nature of these symptoms.

3. When the luetic patient presents no nervous disturbance of any kind, the physician should perform lumbar puncture in order to ascertain that no latent meningeal reaction is present. It may be proposed under two different conditions: (a) In the case of a patient under the physician's care, the author believes it necessary, after the first three years of treatment, to carry out lumbar puncture as a routine procedure, in the course of the fourth year. If positive, the treatment must be continued until it disappears; if negative, the examination should be repeated in the tenth year, treatment according to the general rules to be kept up between the two punctures. (a) In case of a patient who consults the physician as to his condition, the author believes that if he presents no nervous disturbances and has not reached the fourth year, lumbar puncture may be postponed until that time, without abandoning the treatment usually applied during these three first years. If the patient calls between the fourth and tenth year, lumbar puncture should be performed as a routine procedure; if he calls after the tenth year, it should be performed, but less necessarily so than between the fourth and tenth year. The author's statistics show that after the tenth year, over 75 per cent of positive reactions are accompanied by a clinical nervous disturbance which in itself is sufficient to attract the attention of the physician.

4. In the patient presenting indefinite nervous disturbances, without known syphilis, the examination of the cerebrospinal fluid may permit, on the basis of its reactions, to charge to syphilis certain symptoms which otherwise might be referred to some other cause. A distinctly positive reaction of the fluid, in the absence of all nervous or sensory clinical signs, when syphilis alone has been

found responsible, indicates an incipient meningitis and imperatively calls for treatment, to be continued as long as the reaction persists. Sometimes these reactions do not yield until after several years of treatment; occasionally, they persist in spite of treatment, and clinical signs indicating serious lesions make their appearance after a latent stage of variable duration. In favorable cases, the development of the nervous lesion is arrested under the influence of the treatment.

A negative reaction indicates with a fair degree of certainty that no meningitis is developing at the time, but this does not mean that the patient is definitely protected. However, latent meningitis becomes progressively less frequent after the fourth year; and especially after the tenth year, although it may appear at any stage of syphilis. It is also noteworthy that all nervous conditions of syphilitic origin are not inevitably accompanied by meningitis. Certain cases of arteritis or deep gummas, limited foci of encephalitis or myelitis, may develop without modifying the cerebrospinal fluid; and although the majority of nervous processes due to syphilis are accompanied by meningitis and consequently determine reactions of the cerebrospinal fluid, the possibility of these lesions must, nevertheless, be kept in mind, in giving the prognosis of a case of syphilis in which the cerebrospinal fluid is apparently normal. This method is of far-reaching importance. The general adoption of lumbar puncture in syphilis will undoubtedly gradually bring about the disappearance of nervous luetic manifestations, which are certainly the most common and the most dangerous sequelae of the disease.

RESPONSIBILITY OF PHYSICIAN WHERE WET NURSE IS INFECTED BY SYPHILITIC NURSING.—G. Thibierge. *Le Bulletin Médical*, 1919, vol. xxxiii, No. 41, p. 537.

In order to avoid all responsibility in regard to the syphilitic contamination of a wet nurse by a nursling, the physician should keep in mind the following rules: Never permit a child born of syphilitic parents, or of parents seriously suspected of syphilis, to be entrusted to the care of a wet nurse. Immediately remove from the wet nurse's breasts, unless she is already contaminated, all children with syphilitic or highly suspicious manifestations; in the last-named case, resort at once to all measures capable of promptly settling the diagnosis.

It is a matter of common experience that syphilitic individuals, even after timely, energetic, regular, and protracted treatment, may still at the end of several years procreate children contaminated by syphilis and capable of presenting contagious lesions. The proportion of these cases as compared to children who under these conditions are born and remain free from syphilis, is extremely small; so slight, in fact, as not to preclude the responsibility of

marriage and procreation. But it is, nevertheless, sufficient for the wet nurse of a child of syphilitic parents not to be mathematically protected against all contamination. Under these peculiar circumstances, the physician must not expose himself to an unfortunate occurrence of this kind.

PROGNOSIS OF SPECIFIC AORTITIS.—William D. Reid, Boston. *Journal of the American Medical Association*, 1919, vol. lxxiii, p. 1832.

Specific aortitis is a disease of progressive character and of serious prognosis. The weight of evidence is against the power of mercury and potassium iodide alone to produce an arrest of the disease. Intensive antisymphilitic therapy is now being administered with promising results. Every case presenting the symptoms of sub-sternal pain and shortness of breath, not definitely explained by other cause, should be promptly studied as to the presence of specific aortitis. Early diagnosis is imperative. The cases in this study which have received adequate treatment and in which the present condition is known are as yet too few to justify positive conclusions as to prognosis. After a few more years, another study of the records should obtain material of more value as to the end-results.

ARSPHENAMINE VERSUS NEO-ARSPHENAMINE.—Jay Frank Schamberg, Philadelphia. *Journal of the American Medical Association*, 1919, vol. lxxiii, p. 1883.

Neoarsphenamine is less active therapeutically than arsphenamine, but the difference in this respect appears to be largely made up by the discrepancy in the tolerated dose. The author has found it possible to give neoarsphenamine in full doses at frequent intervals without reaction. He commonly administers in appropriate cases 0.9 gm. three times a week in early cases of syphilis. Neoarsphenamine appears to create less commotion in the blood and tissues than arsphenamine. Which compound will ultimately be accorded preference can not be forecast. He does not know of any rigid and extended comparative test of the two compounds on a large series of patients with careful data on the serologic end-results. Such an investigation is now being carried out.

NATURE AND TREATMENT OF ACCIDENTS PRODUCED BY ARSENICAL TREATMENT OF SYPHILIS.—V. Pardo Castello. *Revista Medica Cubana*, Havana, 1919, vol. xxx, No. 6, p. 346.

Three classes of reactions have been observed following injections of arsenical compounds in the treatment of syphilis: (1) Phe-

nomena grouped under the heading of Herxheimer's reaction; (2) phenomena grouped under the title of nitritoid crises, on account of their resemblance to symptoms produced by inhalation of amyl nitrite; and (3) phenomena of intoxication, produced by intolerance of the drug, imperfect technic, or incorrectly prepared and manufactured remedies. The phenomenon described as "neurotropism" either coincides with Herxheimer's reaction or are attributable in numerous cases to the spirochete, but not to the arsenic.

The disturbances known as Herxheimer's reaction may be divided into mild and severe, immediate and delayed, and are summarized as follows: Immediate symptoms: headache (expression of meningitis), vomiting, diarrhea, fever, aggravated eruptions, exaggeration of symptoms in general paralysis and tabes, reactivation of the Wassermann reaction. Delayed symptoms: icterus, glycosuria, and meningitis. This reaction constitutes merely a transitory phenomenon, which does not contraindicate the employment of mercurials or arsenicals; its treatment, on the contrary, consisting in the continued employment of the same, with the precaution that the dose is not rapidly increased in those cases which present very severe phenomena of reaction.

The so-called "nitritoid crises" may likewise be divided into immediate and delayed, transitory and grave phenomena. As a rule, these reactions are immediate and transitory; delayed and grave phenomena are rare, only a very small number of cases being on record. Immediate manifestations are cyanosis, hoarseness, attacks of sneezing, deafness, acute edema, rapid pulse, dyspnea. Late and grave phenomena are represented by serous apoplexy or hemorrhagic encephalitis, a rare manifestation. Nitritoid crises are the most frequent accidents following upon arsenical injections and almost invariably appear immediately after the administration of the remedy. The nature of these phenomena has been much discussed, some interpreting them as due to anaphylaxis, others to toxicity, and the majority to a deficiency of the internal secretions. The arsenical remedies used in syphilis have been shown to possess a marked vasodilator action; when injected into certain individuals whose suprarenal glands do not functionate normally, they give rise to the phenomena described as the nitritoid reaction. The injection of ten to twenty drops of adrenalin solution 1:1000 immediately arrested the nitritoid reaction when present, while a preliminary injection of the same substance prevents the onset of the disturbances. This fact is a therapeutic confirmation of the view which refers the phenomena to the vasodilator action of the arsenicals. Serous apoplexy or hemorrhagic encephalitis is of rare occurrence and apparently due to dilatation of the cerebral vessels. It appears several days after the injection and frequently occurs

in individuals who have presented nitritoid phenomena at the time of administration of the remedy.

The enormous quantity of arsenic which is introduced in a given instant into the circulation, may give rise to actual phenomena of intoxication, either through special properties of the drug, or its technical preparation, or through special conditions on the part of the patient. The drug may have been improperly prepared, or damaged during transportation; it may have been dissolved in an acid or hyperalkaline solution; diluted in a large amount of water; injected a long time after it has been dissolved, or in large doses, or at short intervals. Finally, a cumulative effect may occur in case of intramuscular injections. The patient may have severe degenerative nervous lesions; acute or chronic nephritis; noncompensated cardiac lesions, chronic sclerotic aortitis, or aneurysm; cachexia; dementia or softening of the brain. Alcoholism and perhaps idiosyncrasy also enter into consideration. Errors which frequently become the source of accidents are the following: leaving the drug in contact with the air, for it becomes very rapidly oxidized and transformed into a highly poisonous substance; injecting acid or hyperalkaline solutions, which very frequently give rise to general disturbances and to phlebitis of the vessel into which the injection has been made.

Accurate dosage of the remedy is of great importance for the avoidance of unpleasant manifestations, and so is the repetition of the dose at cautious intervals, so as to guard against accumulation. The latter, with rapid absorption of the drug at a given instant, is now rarely observed, the intramuscular route having been practically abandoned in the employment of these remedies. As regards the contraindications of arsenical medicaments in the treatment of syphilis, there are not many left at the present state of our knowledge. Nervous lesions with advanced degenerations (tabes and general paralysis in the last stage) uncompensated heart lesions, and briefly, the advanced cachexias are absolutely contraindications. Chronic nephritis, tuberculosis, and hypersusceptibility to arsenic (if this exists) constitute merely relative contraindications, meaning that in their presence, arsenical medication may be employed, beginning with very small doses, slowly increasing, and carefully watching the patient.

SERIOUS REACTIONS FROM THE SALVARSAN AND DIARSENOL BRANDS OF ARSPHENAMINE.—Joseph Earle Moore and Frederic E. B. Foley, Baltimore. *Archives of Dermatology and Syphilology*, 1920, vol. xxxviii, p. 25.

Four cases have been described of severe reactions to the salvarsan or diarsenol brands of arspenamine with an unusual blood picture, characterized by leukopenia, eosinophilia and increase in the

large lymphocyte and transitional groups, together with other evidence of destruction of the bone marrow. Salvarsan evidently has both a toxic and stimulating action on the bone marrow, and these effects are, so far as can be determined from examination of such a small number of cases, selective. In a fatal case of salvarsan poisoning there was found at necropsy a markedly aplastic bone marrow, showing degenerated cells and absence of the more mature forms of the myelocytic series. The fatal case showed for the first time, so far as can be determined, approximately the same kidney lesion as that produced in experimental animals by Pearce and Brown.

THE ADMINISTRATION OF ARSPHENAMINE BY RETENTION ENEMA.—
John L. Mandracchia, Brooklyn, N. Y. *Medical Record*, 1920, vol. xevii, p. 144.

The administration of arsphenamine by retention enema is a successful and practical method of giving this powerful drug and therefore the method demands a place in the therapy of syphilis. The slow absorption is an advantage and prevents the production of nitroid crises. In children it is the method of choice. The contraindications to this method are nil. The results obtained by this method are just as good as those obtained with the intravenous method.

TOXIC JAUNDICE FOLLOWING "INTENSIVE" ANTISYPHILITIC TREATMENT.—Thomas J. Lynch, St. Joseph, Mo., and Solomon F. Hoge, Waynesburg, Pa. *Journal of the American Medical Association*, 1919, vol. lxxiii, p. 1687.

After the administration of arsphenamine, some slight symptoms due to the direct toxic action of the drug are generally produced, such as nausea or vomiting, transient diarrhea, and a temperature rise of 1 or 2 degrees. These symptoms usually last for a few hours, and no others occur. Very infrequently, however, after a period of three or four days, symptoms of a profound toxemia develop. The patient presents an abnormal mental condition: irritability and delirium rapidly progressing to unconsciousness, with perhaps convulsions and Cheyne-Stokes respiration. Jaundice may or may not appear. Death usually results in from two to three days. This accident is liable to occur following a single dose of the drug. This condition is explained by William H. Wilcox, in his *Lettsomian Lectures on Jaundice*, as undoubtedly due to an autointoxication such as occurs in acute yellow atrophy of the liver. This group of apparently delayed symptoms should be carefully distinguished from those of acute arsenical poisoning, in which we have vomiting, diarrhea, skin rashes, etc. When these symptoms occur after the giv-

ing of arsphenamine they are probably caused by impurities in the product or by its decomposition. There is an additional class of cases whose frequency of occurrence we are now recognizing. These occur at variable lengths of time following the administration of large doses of the drug with a short interval of time between doses. In the so-called intensive treatment, from 0.4 to 0.6 gm. are given at weekly intervals over a period of from six to eight weeks. After a rest of one month, the course is repeated. During the past few weeks we have been able to observe three cases of toxic jaundice, one of which was fatal, following the intensive administration of arsphenamine. All of them occurred in young adult males. All three patients gave a negative history of previous liver involvement, and each was surrounded by every safeguard possible, namely, physical examination, including urinalysis previous to each injection.

ABORTION OF SYPHILIS.—Lacapère Laurent. *Le Bulletin Médical*, 1919, vol. xxxiii, No. 41, p. 539.

The sterilization of syphilis is not difficult in the incipient stage of the primary infection, during the ten to fifteen days following the onset of the chancre, while this lesion still represents the only localization of the treponema. This abortive treatment should consist of the customary methods of intravenous injections of arsenic compounds. Even at this time, as has been shown by autopsies performed a few days after the appearance of the chancre, some microorganisms have become scattered in remote structures, such as the nerve centers, but these treponemas are not sufficiently numerous to manifest themselves by serologic changes, and they are made to disappear at once by the first arsenical injections. The presence of the veins has not had enough time to cause the formation of connective tissue infiltrates and endoperiarteritis, the histologic manifestations of syphilis which undoubtedly offer a certain resistance against the penetration of the curative agent. The assumption is therefore justified that if the medication can be made to act upon the microorganisms while still localized at the point of inoculation, before the connective tissue and vascular lesions which constitute the chancre have been established, the destruction of the spirochetes will be proportionately easier. As a matter of fact, these microorganisms develop locally and insidiously during the entire incubation period of syphilis, without manifesting their presence by any appreciable change. Undoubtedly, their relatively restricted number and the absence of all thickening of the vascular walls supply the most favorable conditions for the institution of the treatment. Theoretically, syphilis may therefore be treated before it manifests itself by the appearance of a chancre, and medicinal intervention during the period of incubation has still better pros-

pects of permitting the sterilization of the infection than under any other conditions. This institution of treatment before the onset of any clinical symptoms is designated by the authors as the preventive treatment of syphilitic chancre. Their clinical observations serve to confirm the experimental findings so unanimously that anti-syphilitic treatment during the period of incubation may be considered as a practically certain means for the prevention of the infection. Although in some cases a single injection sufficed to accomplish the destruction of the virus, it is advisable to repeat the injections, especially around the date of onset of the primary lesions. This treatment should be applied according to the general rules of treatment of syphilis with arsenic compounds, beginning with the injection of very small gradually increasing doses. The authors emphasize that the preventive treatment of chancre must be reserved strictly for individuals whom there is good reason to consider as infected and who can give proofs for their anxiety in regard to contamination with the syphilitic virus.

A NEW NEEDLE FOR THE INTRAVENOUS ADMINISTRATION OF ANTI-LUETIC MEDICATION BY THE LONGITUDINAL SINUS, GIVEN IN CHILDREN.—T. L. Birnberg, St. Paul, Minn. *Minnesota Medicine*, 1919, vol. ii, p. 425.

Due to the danger of transfixing the sinus and the consequent danger of leakage of salvarsan within the subdural space, the author has prepared a special needle for this purpose. This is simply an 18-20 gauge needle upon which is mounted a sliding bronze sleeve which can be set at any distance from the point of the needle by means of a set screw. On measure the length of the bevel of the point of the average needle was found to vary from 4-32 to 6-32 of an inch, and as the diameter of the sinus at this point was from 3-32 to 5-32 of an inch we can see the necessity of making a needle with a bevel of 45° to avoid transfixing the sinus. Also, much more room is obtained if the needle is inserted with the bevel parallel to the surface of the scalp.

SALVARSANIZED SERUM INTRODUCED DIRECTLY WITHIN THE CRANIUM.—A. L. Skoog, Lawrence, Kansas. *Journal of the Kansas Medical Society*, 1919, vol. xix, p. 295.

In the twelve cases reported, four were vascular types of cerebral syphilis, two tabes dorsalis, one idiot, two tabo paresis and five unclassified neurosyphilis. The clinical results of the treatment showed a marked improvement in two cases, slight in six, and none in two; there was a fatality in two cases. Most of these were in extremis. The laboratory showed, as a result of the treatments, that the Wassermann changed in the blood serum in 50 per cent, in the

spinal fluid in 50 per cent, and the cerebral fluid in 80 per cent. The goldsol in the spinal fluid was diminished in 40 per cent and intensified in 30 per cent; and irregular in the cerebral fluids. This work indicates that there are striking differences, comparing the spinal and cerebral fluids in cases of neurosyphilis. If any differences are manifested in the healthy state it has not been ascertained. The Wassermann reaction was different in six cases and agreed in six. The globulin was dissimilar in six and similar in five cases. The cells were always dissimilar. The goldsol reactions were dissimilar in eight cases and similar in four. This would indicate a possible interference in the channels of communication between the ventricles and subarachnoidean space of the spinal cord.

THE TREATMENT OF SYPHILIS OF THE NERVOUS SYSTEM.—Silvio Canestrini. *Il Policlinica*, 1919, vol. xxvi, p. 908, Sezione Pratica.

The guide to the diagnosis of syphilis of the nervous system is furnished by the clinical signs, the reactions of the cerebrospinal fluid representing an adjuvant rather than the guide itself. The treatment of cerebral syphilis without destructive lesions, as in progressive paralysis, is rather variegated. Besides salvarsan, which is more efficient in nervous syphilis than salvarsan-natrium and neosalvarsan (20 per cent arsenic contents), calomel with bitter almond-oil is employed in the Graz clinics; an excellent preparation is novosurol; other valuable remedies are embarin, enosol, mercurol, cinnamon oil at 40 per cent, and others. Iodide treatment is also to be recommended, and in those cases where rapid and energetic medication is desired, an intravenous injection of sodium iodide may be administered up to 25 grams in a 10 per cent solution at each dose. Klemperer (1915) sometimes gives it immediately after the salvarsan injection. It must be kept in mind, however, that iodide even by the mouth is not readily tolerated by aged individuals, and that it should not be administered even to youthful patients, unless there is increased vascular pressure. Certain authors have tried the injection of salvarsan directly into the intradural cavity, claiming for this mode of application a direct influence upon the nervous system, which in their opinion is not obtainable with the intravenous method. Others, on the contrary, object to endospinal application, believing that it excludes the sterilization of the organism as a whole.

The cases of tabes best adapted to salvarsan treatment are those in which the disease is still in its first, neuralgic stage; existing ataxias may also prove amenable to improvement. But when the disease has reached its final stage, salvarsan is no longer indicated, because it may aggravate the clinical picture. Care must be taken not to give exaggerated doses, especially at the beginning, not more

than 0.15 should be injected, gradually increasing, but never in tabes exceeding the dose of 0.45 salvarsan or 0.60 neosalvarsan. It is, moreover, advisable to keep tabetic patients in bed during the treatment, on account of the instability of the pulse so frequently met with in this disease. The clinical symptoms must be carefully watched after the injection, and overenergetic cures are to be avoided. In view of the danger of hyperthyroidism in tabes, the institution of iodine treatment must be judiciously considered, in order to guard the patient against the development of exophthalmic goiter, in addition to the tabes. Needless to say, specific treatment should be avoided in the forms of pseudotabes due to alcohol or nicotine poisoning.

The results obtained in tabes by combined salvarsan and mercurial treatment are greatly superior to those accomplished by the administration of salvarsan alone. On account of the intolerance of tabetic patients for many mercurial preparations by the hypodermic route, treatment with mercurial inunctions is to be recommended in these cases. Favorable results have been obtained in the last few years with subcutaneous injections of fibrolysin, and in the tabetic crises, up to twenty drops of adrenalin at 1 . . may be administered. Surgical intervention, in the form of resection of the posterior roots, following laminectomy, has also been resorted to of recent years for the relief of tabetic disturbances. This operation was originally devised and recommended by Mingazzini in Italy.

Progressive paralysis is the most deplorable syphilitic affection of the nervous system, and rarely shows the intermissions in the course of the disease which are observed in tabes. Among one hundred syphilitic individuals, there is a percentage of four to five paralytics. The reason why in a small percentage of luetic patients the central nervous system is attacked, whereas in a much higher percentage even of untreated cases it escapes, is probably explained by the theory of the existence of different varieties of spirochetes with more or less affinity for the nervous system (Marie and Levaditi). This theory is supported also by the occurrence of conjugal paralysis and by the fact that mostly those patients are usually attacked by tabes or progressive paralysis who in the course of the disease have not as a rule shown syphilitic affections of the third stage. Also in this disease the intravenous administration of salvarsan has yielded rather scanty results. Attempts have been made to influence the disease by antiphlogistic medication. Specific antitoxins have also been recommended. Trephining of the skull has been tried, but without effect, neither have internal treatment, electricity, and radiotherapy proved advantageous. Nevertheless, an optimistic attitude is a desideratum here as elsewhere in medicine. The view that progressive paralysis is an incurable

disease, is the greatest obstacle to the discovery of an efficient curative method. It is to be hoped that the day is not far distant when paralysis will possess a merely historical interest.

RESULT OF TREATMENT OF NEUROSYPHILIS (GENERAL PARESIS AND CEREBROSPINAL SYPHILIS). REPORT OF PATIENT'S CONDITION FOUR YEARS OR MORE AFTER LEAVING HOSPITAL.—H. C. Solomon, Boston. Boston Medical and Surgical Journal, 1920, vol. clxxxii, p. 60.

A review four years or more after the dismissal from the hospital of ten cases of neurosyphilis who were reported as aided by antisymphilitic treatment is made. Nine of these patients were committed as insane, the remaining case was diagnosed general paralysis but not necessarily committable. Eight cases were diagnosed general paralysis, two as cerebrospinal syphilis. It should be added that the diagnosis of cerebrospinal syphilis was changed from general paralysis on one of these two only because he cleared up under antispecific treatment. The mental symptoms were those of paresis. Of the eight cases diagnosed general paralysis, five are now living at home. Three are apparently entirely well, two while not well are able to care for themselves and live a normal life in the community. Two are dead and one is in a hospital. One of the two who died had a fair remission with economic efficiency for eighteen months and had all laboratory reactions negative at one time. The one who was in a hospital had a remission of three years' duration. Two cases were diagnosed cerebrospinal syphilis (nonparetic), but with marked mental symptoms. One left hospital apparently entirely normal and with negative laboratory signs. He has been lost from view. The other is now serologically negative and mentally normal after four years. Of eight cases diagnosed general paralysis, three are apparently entirely well after four years; two are well enough to live outside and care for themselves; one had remission of more than three years' duration, now in hospital; two are dead, having had remissions of eighteen months each. Of two cases diagnosed cerebrospinal syphilis with mental symptoms, one is lost from observation, the other is mentally normal and serologically negative. This report leads the author to feel that it is possible to help a portion of cases of general paralysis or cerebrospinal syphilis with mental symptoms and that intensive, systematic treatment will change the prognosis of general paralysis. It was not the intention to discuss the percentage of cases of general paralysis that could be helped when this report was first made in 1916, but it did represent a fair percentage of the cases that had had intensive treatment. At this time the desire is merely to bring this report up to date. It does seem encouraging, however, that the

results have been so good for such a relatively long period. The author concludes that the majority of cases of syphilis of the nervous system, whether the so-called cerebrospinal syphilis, tabes dorsalis, general paralysis or other forms, are entitled to treatment, and if this is done thoroughly, intensively and systematically the results will be gratifying. The form of treatment, mercury, iodide, arsenic intraspinal and intracranial injections, and the amounts will necessarily depend upon the condition of each individual patient.

SYPHILIS OF THE PRIMARY AIR PASSAGES AND OF THE EAR.—J. A. Pan-sardi. *Revista Medico-Cirurgia do Brazil*, 1919, vol. xxvii, No. 4, p. 109.

Syphilis and tuberculosis are extensively represented as grave affections with a chronic course in the upper respiratory passages and in the ear. The practical importance of the study of luetic manifestations clearly results from the great frequency and gravity of the disease, as well as from the sometimes very remarkable effects exerted by timely specific treatment on the majority of these phenomena. The latter are divided into three large groups: (1) Lesions of acquired syphilis in the various stages. (2) Lesions of congenital syphilis. (3) Lesions of syphilitic origin but not of syphilitic character, corresponding to the parasyphilis of Fournier. The manifestations of acquired syphilis are divided into primary, secondary, and tertiary; those of congenital syphilis, into premature and remote. Parasyphilitic lesions in the sense of Fournier are those local manifestations which may be likewise of syphilitic origin but not of syphilitic character, although amenable to specific treatment. The localizations discussed by the author are the nose, the oral and nasopharyngeal cavity, the larynx, and the ear.

Nasal Syphilis.—The literature contains about twenty cases of *primary* nasal syphilis. All solutions of continuity in the nose, without distinction, may give rise to luetic infections, the onset of which is usually not observed by the physician. Later on, objective symptoms predominate, in the form of deformity and swelling, whereas the symptomatology of intranasal syphiloma consists primarily of subjective or functional disturbances. The literature contains cases of syphiloma of the turbinates or of the external wall of the nasal fossæ. Abscesses of the septum, partial or total ethmoiditis, and abscesses of the lacrymal passages are possible complications of endonasal syphilis. Swelling, hardening, ulceration, cervical and preauricular glandular enlargement, are the principal diagnostic features. Differentiation from gumma is sometimes difficult, but the gumma is less localized, the ulceration is more extensive, and the bony framework is sometimes involved.

One of the first *secondary* manifestations of nasal syphilis consists of nasal catarrh, unilateral or especially pronounced on one

side. The external portion of the nose presents the manifestations of cutaneous lues, in the form of papules, pustules, or crusts; to which may be added cutaneomucous lesions with erosions of variable depth. Mucous patches are usually present, resembling those of the buccal mucosa, but much less common (eight times in 176 cases, according to Deville.) These patches have their seat of predilection at the entrance of the nostrils. The *tertiary* manifestations may give rise to deep lesions which promptly become irreparable, and, moreover, may become transmitted to the meninges and the brain; the resulting disturbances manifesting themselves from two to five years after the infection. The fundamental lesion of tertiary nasal lues is the gumma, which may occupy any point of the nasal fossæ, or be found in order of frequency on the septum, the nasal floor, the vomer, the ethmoid bone, the ascending ramus of the upper jaw. The bony structure is always the seat of deep lesions taking a rapid course. The changes caused by the destructive osteocartilaginous lesions vary, according to the point of origin of the gumma, and can be divided into skeletal lesions (septum and bones), palatine lesions, and sphenoethmoidal lesions.

Syphilitic Lesions of the Pharynx and Nasopharyngeal Cavity.—*Primary* lesions in the form of syphiloma have been observed on the isthmus of the fauces, while the pharynx and the tonsil are frequently the seat of syphilitic ulceration. The *secondary* phenomena are represented by the following manifestations: Syphilitic erythema of the pharynx; flattened condylomas or mucous patches, secondary ulcerations. In case of involvement of the tonsils, the submaxillary glands are enlarged. In the *tertiary* manifestations, a distinction must be made between the lesions of the mucosa and those of the bony framework. The lesions of the mucosa consist of gummatous infiltration, usually followed by superficial or deep ulceration, so that a distinction can be made between a mild and a perforating form. The gummatous process may manifest itself in the form of a true tumor (gumma), with its seat of predilection on the posterior portion of the pharynx or on the hard palate. The presence of ulcerations predisposes to the formation of scar tissue and adhesions of the palatine vault and pharyngeal wall. The destructive process may lead to more or less extensive necrosis of the hard palate, the palatine bones, the vomer, and even the first cervical vertebræ. Fatal hemorrhages have been observed in a few cases, through erosion of the large regional blood vessels. Atrophy of the lingual tonsil is considered by some observers as an indication of tertiary syphilis, this atrophy may be scattered in irregular spots, or it may be limited to the middle portion, or it may be diffuse over the entire tonsil. The back of the tongue appears smooth, through the disappearance of the adenoid tissue.

Syphilis of the Larynx.—Knowledge of this condition begins with the introduction of the laryngoscope. Primary syphilis has not yet been recorded in the larynx, perhaps on account of the depth of the organ. The secondary lesions of laryngeal syphilis are represented by catarrhal luetic laryngitis or syphilitic erythema; macules and papules; mucous patches, on the epiglottis and the aryepiglottic ligaments, the true vocal cords. The tertiary manifestations spare no tissue, affecting the mucosa, cartilage, tendons, muscles, and nerves. Subsequent strictures are apt to follow. Papulonodular eruptions or tubercular syphilides; diffuse gummatous infiltrations; perichondritis; gummas of the submucous tissue; gummatous syphilis of the vocal cords; gummatous myositis, and paralysis of the intrinsic muscles of the larynx; all of these are manifestations of tertiary laryngeal syphilis. The localization of congenital lues in the larynx is uncommon, consisting of superficial chronic laryngitis, hypertrophic laryngitis (usually unilateral) deep ulcerative laryngitis, and an intermediate form, namely chronic interstitial laryngitis.

Syphilis of the Ear.—Primary lesions of the external ear are rare, and are accompanied by considerable enlargement of the neighboring lymph glands. In the majority of cases the involvement of the ear in secondary luetic manifestations is of slight importance; the pharyngeal and rhinopharyngeal lesions giving rise to more or less marked symptoms of tubal stenosis, which do not differ clinically from those caused by simple rhinopharyngitis. However, in certain rare cases of secondary lues, the manifestations on the part of the external auditory meatus and concha present the same characteristics as analogous lesions observed in other cutaneous areas. Occasionally, labyrinthitis makes its appearance and may take a rather serious course. The scanty anatomopathologic statements in the literature also show the existence of changes in the middle ear. The frequency of middle ear affections, especially in the secondary forms, is accounted for by the changes caused by syphilis in the pharyngeal and buccal cavity, as well as by the internal administration of potassium iodide and the abuse of alcohol or tobacco. The otitis interne of acquired syphilis may be unilateral or bilateral, and may appear at different periods of the infection, being most common in the secondary stage (six months to two years after the infection). As a rule, the labyrinth is the seat of specific inflammatory processes, such as small cellular infiltration of the endosteum and the membranous labyrinth; hemorrhages; new formation of connective tissue; degenerative processes such as atrophy and degeneration of nerve cells, calcium deposits, etc. The functional disturbances are identical with those of other types of internal otitis. The internal ear is frequently the seat of one of the most serious manifestations of late congenital

syphilis, capable of inducing deafness, which rapidly becomes complete. The labyrinthitis of congenital lues usually begins at the age of eight to twenty years and preferably affects the female sex. The course of congenital luetic labyrinthitis is analogous to that in acquired syphilis, although slower; it is usually determined, in individuals having congenital syphilis, by sometimes very trifling causes, such as rheumatic factors or acute intercurrent affections.

THE USE OF FLOCCULE-FORMATION REACTIONS TO CORROBORATE THE WASSERMANN TEST.—Ross J. MacCann, New York City. *The Journal of Laboratory and Clinical Medicine*, 1919, vol. iv, p. 742.

In many diseases, and particularly syphilis, the serum of a patient thus afflicted, when mixed with colloidal solution of lecithin or sodium glycocholate, forms a flocculent precipitate which may be seen macroscopically.

The first method investigated was that of Porges and Meier. Nineteen serums, eight positive and eleven negatives were used in this test. Where inactivated serum was advocated by the author, we also used activated serum, the results obtained being nearly similar. The specificity of this method is low, approximately 45 per cent of the positive serums gave negative results, and 20 per cent of the negative serums gave positive results.

The second method was that of Elias, Neubauer, Porges and Salomon. The results obtained were slightly better and more accurate than the first method, but the advantages of this method are greatly lessened by the fact that only clear serums can be used in the tests.

The third method tested was that of Klausner. Results obtained were confusing and nonspecific.

The fourth method used was that of Herman and Perutz. Results obtained were distinctly better and more accurate than in any of the other methods tested, but were only partially specific. Approximately 70 to 75 per cent of the positives gave positive results, while two of the eleven negative serums gave distinctly positive results, and one was extremely doubtful, due to a heavy clouding.

Summarizing his observations on the results obtained in the tests of the above methods, it was quite obvious to MacCann that, possibly with the exception of the Herman and Perutz method, these methods can not be used with any great degree of certainty to corroborate the Wassermann test, and especially so in those cases where the Wassermann gives a doubtful or anticomplementary result.

SYPHILITIC POTT'S DISEASE.—A. Aimes. *Le Progrès Médical*, 1919, No. 22, p. 214.

The author on the basis of personal investigations emphasizes that syphilitic spondylitis is not sufficiently known and probably

more common than is usually assumed. In view of the special predilection of syphilis for the bony system, the question arises if the apparent rarity of cases of syphilitic Pott's disease is not referable to errors in diagnosis. Although specific spondylitis may occur in congenital syphilis, this is uncommon, syphilitic disease of the vertebræ being more frequently observed in acquired lues and in the course of the tertiary stage. Nearly all the published cases concerned men. The usual localization is cervical, in about one-third of the cases. The lesions vary from simple superficial osteoperiostitis to grave destructive lesions with sequestra. Small sequestra have been found in gummas, or in the pus of abscesses which are rather uncommon and suggestive of Pott's disease. The vertebræ are especially affected at the level of their bodies, but attention must be called to the production of syphilitic exostoses which represent a valuable diagnostic feature. Lesions of the meninges and the spinal cord have also been reported, as well as cases of neuritis. Clinically, the disease behaves like tuberculous Pott's disease, and the syphilitic origin can be recognized only by a careful study of the symptoms. The first and most important clinical sign is pain, which in contradistinction to the pain of Pott's disease is not relieved by rest. The patient is apt to complain of pain on awaking in the morning, and occasionally there are nocturnal painful exacerbations which lend a syphilitic aspect to the disease. Radiating pains are not uncommon. Vertebral deformity is less frequent than in tuberculous spondylitis, and may be due either to bony destruction, as in Pott's disease, or it may appear in the form of an irregular swelling due to syphilitic osteophytes. Contractures are common, and as the disease is preferably situated in the cervical region, the patients attitude is that of suboccipital or cervical Pott's disease, with torticollis, rigidity of the neck, and so forth. Existing abscesses are less voluminous than in tuberculosis. Reflex and sensory disturbances are variable (hyperesthesia or anesthesia).

The prognosis depends on the timeliness of the diagnosis, for properly treated cases usually recover in good condition, but if the syphilitic character of the disease is not recognized, the outlook is aggravated by serious complications. The cases with posterior lesions are the most favorable, the solidity of the spine being only slightly affected, whereas anterior syphilitic Pott's disease with destruction may be extremely serious. The complications consist especially in paralysis, localized in a single upper or lower limb, or bilateral. Fournier observed dysphagia due to a retropharyngeal gumma. This disease has been known to lead to sudden death.

The diagnosis must be based on the patient's history and on the association with other syphilitic lesions. Aside from the charac-

teristic pain and deformity, as well as the presence of gummas, the Wassermann reaction must not be neglected. Radiography may prove extremely valuable in verifying the features of the bony swelling. Specific osteophytes differ markedly from a Pott's gibbus. Real diagnostic difficulties arise only when the two diseases are associated in the same patient. It is always of advantage to discover the existence of syphilis in a case of incipient Pott's disease, in order to treat it and thereby improve the prognosis. The treatment is easy, and consists in immobilization of the vertebral column, according to the localization of the lesions, and in the institution of specific treatment, which will yield good results in the majority of the cases.

URTICARIA PROBABLY DUE TO SYPHILIS.—Lester Hollander, Pittsburgh. *Archives of Dermatology and Syphilology*, 1920, vol. xxxviii, p. 55.

Syphilis may produce urticarial skin manifestations. Urticaria may at times be due to syphilis. Two cases of urticaria were cured by antisymphilitic treatment.

MANIFESTATIONS OF SYPHILIS IN THE NOSE AND THROAT.—Arthur H. Geiger, Chicago. *Illinois Medical Journal*, 1919, vol. xxxvi, p. 233.

Snap-shot diagnosis in throat trouble is wrong and syphilis should be considered before treatment is advised. Noses and throats should be examined with the best of light by general practitioners. Specialists usually use good illumination. Careful questioning as to luetic infection should be the rule in chronic nose and throat affections, especially if contemplating operation. Proper antisymphilitic treatment has shown good results on the lesions of nose and throat syphilis.

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Original Articles

A SYMPOSIUM*

ON THE CLINICAL RECOGNITION OF SYPHILIS AND THE SYPHILITIC

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*Presented to the St. Louis Medical Society, Dec. 2 and 9, 1919.

I

**INTRODUCTION—SOME PRINCIPLES IN THE CLINICAL
RECOGNITION OF SYPHILIS AND THE SYPHILITIC**

BY WILLIAM WASHINGTON GRAVES, M.D.

THERE are no problems before the medical profession at the present time of greater importance to the individual and to the race than those connected with syphilis. To solve these problems will require the united work of the medical profession, the educator of public opinion, the sociologist and the philanthropist. Years before the recent great advance in our knowledge of syphilis, Sir William Osler gave to the medical profession this commandment and promise—

“Know syphilis in all its manifestations and relations, and all other things clinically will be added unto you.”

Through clinical observation and pathologic studies during the centuries which have elapsed since syphilis invaded the civilized world, our knowledge has grown bit by bit from period to period until today some of our conceptions of syphilis may be thus epitomized:

That syphilis is a chronic, infectious disease permeating all branches of society; that neither age, nor sex, nor social position, nor chastity renders one immune to its manifestations; that at any period in the life of the infected individual its manifestations may recur, and we are therefore unable to know its termination; that its symptomatology is as broad as special pathology, no organ or tissue in the body being exempt from its manifestations; that there are few diseases it may not simulate, and none that it may not modify; that it is rarely fatal, but its indirect mortality is believed to be very high—how high is as yet indeterminable; that it lowers one's general resistance thus predisposing to other diseases and often complicating them; that no other infectious disease is followed by such distressing sequelæ, chief among which are deafness, optic atrophy, tabes and general paresis; that it is often communicated in the marital relation and even by those whom we believe we have cured; that it differs from all other diseases in its pernicious effects

upon the descendants of its victims in causing a frightfully high antenatal mortality, and in depriving many of the offspring of a healthy birthright.

Because we have no means of definitely knowing, save by reinfection, the termination of syphilis in any individual who has acquired it, all such individuals for clinical purposes, must be considered syphilitics. Because syphilis is a chronic, infectious disease permeating all branches of society; because it has protean manifestations and sequelæ; because it lowers the general resistance of the infected individual; because it predisposes to, simulates and modifies other diseases; because it affects the immediate progeny and later generations, the recognition of syphilis and the syphilitic is a matter which deeply concerns the infected individual, his descendants, the state, and the physician.

Syphilis is the only known systemic disease capable of engendering such widespread tissue reactions that almost any organ, or tissue in the human body may be the seat of its symptomatology. A few of these reactions are the subject of discussion in this symposium. Others might be added, but it is believed that those here discussed may serve to *awaken anew the one-time interest in the clinical recognition of the disease in its protean manifestations and also to awaken interest in the clinical recognition of the individual, who by reason of his one-time infection joined the world army of syphilitics.*

No place has been found in this symposium for laboratory methods in the clinical recognition of syphilis and the syphilitic. The reason for this omission should be apparent to every thoughtful physician. He must be conscious of *the growing danger to many in the profession of becoming mainly interpreters of laboratory symbols and reports.* Nevertheless, the development and utilization of laboratory methods in the course of years have been largely responsible for the recent great advance in our knowledge of syphilis, and these methods are now indispensable in our studies of syphilis and the syphilitic, but they represent only one part of the study of the individual. The danger lies in using these methods to the exclusion of all others and in thus preventing on the one hand the recognition of syphilis, or the syphilitic in the presence of a negative laboratory report, and on the other hand in establishing the positive recognition of syphilis or the syphilitic in the presence of a positive laboratory report. We have only to remember how the clinical recognition of

pulmonary tuberculosis was impeded for a number of years following the discovery of the tubercle bacillus. The same danger confronts us now in the clinical recognition of syphilis and the syphilitic, when undue reliance is placed upon the laboratory for diagnosis. Just as in former years we forgot how, or rather failed, to study the whole individual, when searching for the tubercle bacillus, so now in the absence of a positive Wassermann reaction, we are either apt to overlook manifest signs or to study inadequately the whole individual, and thus fail to recognize his disease.

Recognizing the limitations of laboratory methods is to estimate them at their true worth, but as a profession we do not recognize their limitations, and because of this fact we are apt to go backward rather than forward in our studies of syphilis and the syphilitic.

So manifold are the manifestations of syphilis, and so widespread is its distribution among civilized races of man that the physician is compelled to consider the possibility of syphilis either as a causative or complicating factor in almost every individual who presents himself for diagnosis and treatment. The physician in his work must, therefore, constantly ask himself these questions:

1. *Is the individual a syphilitic?*
2. *Is the disease picture presented by the individual that of syphilis?*
3. *Is the disease picture presented by the individual complicated by syphilis?*

Each of these questions must frequently arise in the physician's mind in his daily contact with the sick, but not one of them, excepting the first, can be answered in many cases by the laboratory alone, but all of them can be answered in most cases by the study of the *whole individual* in all this phrase implies, and then, and not until then, should the aid of a laboratory be sought and utilized in diagnosis. It is much easier *to decide* (?) what is wrong from the complaints of the patient, or from his more prominent physical signs—to call it eye-strain, epilepsy, floating kidney, sacroiliac disease, gastritis, neurasthenia, hysteria, rheumatic ocular palsy, gastric neurosis, a functional heart disturbance, a muscular rheumatism, a neuralgia, a bilious attack, a vertigo, a sciatica, a gouty diathesis, an autointoxication, a focal infection, an endocrine disturbance and so on without number than *to make a study of the whole individual*. Such study takes time, and, strange to say, is

often regarded as wholly unnecessary in this day of specialism and laboratory short-cuts to diagnosis. Then, if this is true, our failure to study the whole individual may well be said to be the most serious impediment in the clinical recognition of syphilis and the syphilitic. By the study of the whole individual is usually implied all that we can learn from the family history, the personal history, the history of the present trouble, its course, and a searching physical examination. Because syphilitic manifestations are frequently found in the consort and progeny of the syphilitic, our clinical conceptions must be so enlarged as to embrace a study of these. Just as it is impossible to exclude by a negative history, absence of surface manifestations and a negative laboratory report, the presence of syphilis in the individual, so it is impossible to exclude it by the same means in the consort and in the progeny. It is not sufficient to recognize syphilitic manifestations in the husband, in the wife or in the child, but finding such in any one of them, if we would really study and know syphilis, we must study every member of the family and in doing this, we shall be able to control by actual observations hearsay testimony, which we have heretofore recorded as facts concerning family history and the health of the husband, wife, and child. A consideration of the whole individual as here defined and so enlarged as to embrace a study of every member of the family will enable us to secure definite data, from which the clinical recognition of syphilis and the syphilitic will be made more frequent and more certain than heretofore.

Your confreres participating in this symposium earnestly request its liberal discussion by the members of this society, to the end that more light may come to the profession in its struggle against syphilis—the insidious, hydraheaded enemy of man!

DISCUSSION

Dr. B. S. Vedder.—In opening the discussion on Dr. Graves' paper it is my privilege to express the appreciation of the society to Dr. Graves for arranging this symposium. I think the number present tonight expresses better than anything I can say the interest in this subject.

Dr. Graves, first of all, brought out the importance of syphilis. I think few of us really realize that 10 per cent of the population of the United States is syphilitic; of course the actual amount varies in different social classes and races. Those of you who are at all interested in the public health aspect of syphilis would enjoy and profit by reading the recent book from this standpoint by Vedder of the Public Health Service. I hope that none of you

receive the impression from Dr. Graves' paper that he minimizes the importance of laboratory work in syphilis. We all know Dr. Graves and his laboratory researches in syphilis. What he is emphasizing is the importance of the recognition of syphilis from the clinical standpoint alone.

I am sure from what the various speakers who have given us talks tonight have said we do not have to wait until next week to realize that syphilis may produce pathologic changes in every organ and tissue in the body, hence its importance from the clinical standpoint. I wish, however, that Dr. Graves had included in his symposium a paper on the relationship between laboratory findings and the clinical picture. For when all is said and done, as Dr. Graves brought out in his paper, the fact remains that all of the advance in syphilis has been the result of laboratory work in our own time and generation.

The subject from the clinical standpoint is the thing that I hope will be thoroughly discussed this evening. Examining a patient, the first thing to be decided is whether or not the individual is syphilitic, and secondly, if the patient is syphilitic, whether or not the disease or condition which the patient presents is due to the syphilis. If laboratory work has led us astray, it has been chiefly in regard to this second point; for, granted that the patient is syphilitic, it is by no means certain or positive that the condition he comes for is one due to syphilis. Again and again we see patients coming with some obscure condition, a Wassermann test is made, and if it is positive, we are at once apt to conclude that the condition is due to syphilis. Again and again we find tuberculosis in syphilitics and the question of calling the pulmonary lesion syphilis practically never arises, as tuberculosis is such a common and well-recognized disease. While the presence of a syphilitic infection may lower the resistance to any other infection and thus bring about a relationship between the two, such as we see in the association of tuberculosis and syphilis, it is most important that the two diseases be differentiated, and it is just here that the recognition of syphilis from the clinical standpoint is most important.

II

THE INITIAL LESION AND ITS DIFFERENTIATION FROM OTHER LESIONS

BY JOSEPH GRINDON, M.D.

DOWN to our own day, the recognition of syphilis rested upon clinical evidence alone, and while the diagnostic frontier was gradually pushed farther and farther, such extension could only result from the correlation of clinical conclusions, depending in turn upon the gradual accumulation of observed facts. Progress was necessarily slow, and doctrines elevated to the rank of dogma were proportionately secure from attack. Now, however, that microscopy, and especially serology, have come to our aid, new territory is daily being added to the domain of King Lues, while none but a Bourbon among clinicians would maintain that his conception of the symptomatology of syphilis had attained finality.

Shall we still hold to Ricord's dictum, that, apart from hereditary and conceptional forms, chancre is the obliged exordium of syphilis, or shall we seek in some newer and more liberal creed the explanation of those cases by which we have so often been mystified, in which undoubtedly syphilis existed despite total absence of any evidence or record as to its mode or site of entry?

For the present at least, accepting as we must, the reign of law in pathology as in other realms of Nature, let us hold the faith undefiled, explaining apparent exceptions by (1) the incidence of the above-mentioned hereditary and conceptional forms, (2) the fact that extragenital lesions often pass unrecognized, and are therefore easily forgotten, (3) that even genital lesions may be inconspicuous, atypical, and painless, (4) the fact that lesions of the male urethra, cervix, rectum, or nasal cavities may remain undiscovered or unrecognized, (5) that the same is often true of lesions more obviously situated in women, (6) the fact that some patients are possessed of memories capable of convenient lapses.

Let us then refresh our minds as to the characters of primary syphilis.

A typical chancre is probably, to use a sporting phrase, more "true to form" than any other lesion. As Ricord inimitably puts it, it wears a characteristic physiognomy.¹ The true chancre is

usually single, but occasionally multiple; in about 20 per cent, say Hallopeau and Fouquet,² while Ross, at Camp Green, N. C., found only 9 per cent.³ Occasionally they are numerous, thus Ricord saw 19 at the penoscrotal angle. and Fournier cites a woman with 7 chancres on the left breast and 16 on the right. R. W. Taylor showed that successive chancres are less rare than was supposed. When we remember that chancre is usually antioinoculable for the first ten or eleven days, we wonder that they are rare at all. These things serve to remind us that syphilis is always at first a local disease.

The period of incubation is roughly, three weeks, the average being more exactly fixed at twenty-five days, with extremes at fifteen and forty-five days. Exceptions have been noted, as in a well-substantiated instance reported by Puche, with an interval of eighty-one days. Older records of prolonged incubations may safely be disregarded. Certain intercurrent diseases, such as typhoid and smallpox, seem to retard the appearance of the chancre.

At first, a small, reddened, itchy spot presents a rapidly excoriating centre, soon covered by a light crust. A macroscopic diagnosis is at this time impossible, but the spirochaeta may at times be found in the expressed serum. Little by little the lesion extends at its periphery, and becomes a round or oval, sharply defined, superficial, flat erosion, level with the surrounding surface, or, if anything, rather elevated than depressed. Its borders are regular. The eroded center is of the color of raw meat and granular, with a slight serous or serosanguinolent exudation. There is slight tenderness, but, in most situations, no pain.

Soon its dimensions attain approximately to those of a silver dime, the borders become more sharply marked, and a new and more distinguishing character appears, namely, that of induration.

The lesion is by now a papule. Grasping it between thumb and finger, one detects an intradermal infiltration coinciding and continuous with the lesion. This induration, while rarely absent, may vary greatly in degree, and consequently in ease of recognition. Thus it may be cartilaginous, card- or parchment-like, or even papery. Induration is habitually greater at certain regions than at others. On the penis, it is deeper and denser in the balanopreputial furrow and at the meatus, and thinner on the dorsum of the glans. Montgomery⁴ explains this by the different course of the vessels in each of these

regions, and the well-known vascular predilection of luetic infiltration.

While the phenomenon of induration is forever linked with the name of John Hunter, it was known to Jean de Vigo, and to Ambroise Paré, who says, "If there be an ulcer of the yard, and there remain hardness at its site, this infallibly shows that the patient has the pox," and Thiérrey de Héry at the same time calling attention to another well-known sign, wrote in 1660, "It is indeed true, that the most certain signs of the pox are seen when during or after the presence of ulcers upon the shameful parts (especially such as are callous and hard at their roots) there appear tumors of the groins which return into the body without suppurating."

The chancre heals in about a month, Klauder⁵ found the average in a series of 115 penile chancres to be 34.4 days.

Induration usually appears during the second week, less often during the third from the appearance of the sore. It persists after healing, but has usually disappeared by the end of the second month, although occasionally present for several years. Ricord once found it after thirty years.

In the majority of cases, there being no deep destruction, chancres heal without a permanent scar. In ulcerating cases, however, there remains a depressed cicatrix, at first pigmented but later blanched.

The adenopathy of primary syphilis is characteristic both in its appearance and in its course. The nodes are enlarged, but remain discrete and mobile, with little or no tenderness. The skin over them retains its normal feel and color. As Fournier says, it is not so much an adenitis, as a plastic adenopathy. Generally, the enlarged nodes, although bilateral, are best marked on the side of the chancre, although sometimes the contrary is the case, owing to crossing and irregular distribution of lymphatic vessels. The phenomenon becomes apparent at about the end of the first week. Resolution is slowly progressive, and rarely complete, thus furnishing an aid to the diagnosis even of late lues. In about 2 per cent⁶ of all cases there is suppuration, due to secondary infection. Fournier distinguishes between the *clinical* adenopathy just described, and the anatomic adenopathy simultaneously involving deeper and hidden gland groups.

It is important to remember that something more than 6 per cent of all chancres are extragenital. Their relative importance is how-

ever greater than this small percentage would represent, since they contribute a large share of unrecognized and therefore disastrous cases. Their physical attributes vary somewhat according to their situation. About 75 per cent are cephalic.

When the sore is on the upper lip, we must look for the node under the jaw, when on the lower lip, it will be under the chin. Sometimes both are involved in either case. Tongue chancres are accompanied by submaxillary adenopathy, but these and sores anywhere within the mouth often are attended by a diffuse, doughy, and highly inflamed swelling of the entire region, attended often with much pain, due to secondary infection from the rich flora of the mouth. Tonsillar chancres, of which I have encountered ten cases, are generally at first mistaken for diphtheria. One should note that they remain unilateral, show a characteristic induration, and lymphatic swelling near the greater cornu of the hyoid on the same side.

Cheek and chin chancres usually deserve the name of "Barber's chancre" although some are attributable to kissing. They are generally pustulocrustaceous, and often more than one. They may so closely resemble epithelioma, that especially in an aged person, the latter diagnosis may be made. The lymphatic engorgement is submaxillary.

Chancres of the trunk affect mainly three situations, the suprapubic region, the neighborhood of the anus and perineum, and the female breast. The first named are purulent and crusted, and often attain to huge dimensions. Anal chancre simulates a fissure, but its borders are everted and hard. When within the sphincter, it is hidden, but on stretching the muscle, one sees a red, varnished erosion, often formed of two segments which close together, as Fournier says, like the leaves of a book. Rectal chancre, which when discovered presents the usual features common to chancres elsewhere, usually masquerades at first as a case of piles, often only a retrospective diagnosis being made. The only case observed by me was in the person of a physician. Anal and perianal chancre is accompanied by inguinal adenopathy, but the lymphatic involvement in rectal lesions often remains hidden, although here too the inguinal glands may be involved by anastomosis. Chancre of the mamma, often multiple, is generally seated at the nipple or areola. It is usually eroded and crusting, with axillary swelling. Gaucher saw a chancre on the back of the neck, and I once encountered one in

the middle of the back, at about the level of the inferior angles of the scapulæ.

The obstetric chancre occupies the right index, near the nail. Sometimes (Taylor's whitlow chancre) the finger end is at first tensely swollen, dark red, and very painful, while later there is ulceration with hard, prominent borders. These cases are often prolonged over several months and sometimes attended with loss of the nail. At other times there is massive and painful induration following the nail fold in the manner of a "run-around."

I trust that an indulgent audience will remember that the subject assigned me was most trite, and that on the other hand anything like a complete presentation is impossible within the brief limits determined upon. There are several aspects of the topic that I have not so much as touched, but here I must leave the matter.

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III

THE EARLY AND LATE SKIN AND MUCOUS MEMBRANE REACTIONS

BY MARTIN F. ENGMAN, M.D.

IT is well known through the investigations of Metchnikoff and Roux, Neisser, and others, that probably within ten days after the initial inoculation, the virus of syphilis becomes generally distributed to the various tissues of the body and antedates the objective appearance of the first localization, called the chancre, by one to two weeks.

Subjective symptoms may occur during this time, but the localization at points of distribution in the skin is not usually observed for from sixty to one hundred days after the initial inoculation. In studying the subject of syphilis from a given standpoint one must visualize the general distribution of the virus to all tissues of the body through the blood stream and that in some tissues it proliferates and grows, while in others it may lie in a dormant or latent condition and die out.

To conform the various clinical phenomena of syphilis we must admit that the virus runs in special strains which have an affinity for special tissues. Those strains that have a dermatropic affinity produce the most pronounced cutaneous eruptions in the early and late stages of the disease. Other strains, particularly those of a neurotropic affinity, obviously produce fewer and milder colonies of localization on the skin. After the virus has entered the blood stream, emboli are carried to the cutaneous tissues, landing generally in a grouped manner in the terminal distribution of the skin vessels to produce certain characteristic eruptions.

The earliest of these is seen as a red spot upon the skin and is called the syphilitic roseola which is frequently accompanied by constitutional symptoms. These red spots may disappear or may devolve into the typical lesion of syphilis, the papule.

The papule is the characteristic, essential, and fundamental lesion of syphilis. It is also the culminating lesion and completes the cycle of the spirochete in the tissues. The spirochete lands in the skin or other tissues in one of the terminal vessels, and there, through its influence, induces the formation of plasma cells probably from the

lymphoid cells of the part, as these cells can be seen in various stages of evolution and involution from the lymphoid cell to the plasma cell, the latter being the essential cell of all granulomata, particularly of syphilis.

Naturally the fixed connective tissue cells of the part are stimulated into proliferation and add their cellular elements to the new formation. The spirochete lying in the perivascular tissues or walls of the small vessels, produce there endovascular and perivascular changes frequently with obliteration and occlusion of the vessels. Giant cells are formed as they usually are in granulomata and the homogeneous changes in the vessels produce the appearance of giant cell formation (Fordyce). Thus through the piling up of these new cells in the upper part of the derma, a lesion is formed which juts outward in the course of least resistance and pushes the overlying epidermis outward forming the objective lesion of syphilis, the papule.

From the outward pressure exerted by this lesion, the epidermis is broken in its upper layers, forming the collarette about the lesion. Other changes that may occur in this papule are purely from accidental and intercurrent causes, such as the scale upon the lesion from the drying of the exudate and the epithelial cells which are exposed to the air by the fracture of the upper protective horny layer.

If the papule is studied with proper staining, many spirochetes will be seen scattered in clusters in the lesion and at the points of greatest cell formation. Whether the patient has been treated or not, the early lesions tend to disappear *in situ*, leaving a pigment spot, while in some instances new lesions may occur in other locations, thus demonstrating the fact that something must be formed at the site of an eruption to destroy or repress the specific action of the spirochetes—probably an immunizing body. This immunizing body does not seem to be at first, at any rate, in the blood stream in any quantity, if at all, as new lesions may be formed while old lesions are undergoing involution, thus giving the clinical appearance of multiplicity, so characteristic of cutaneous syphilitic lesions.

We have thus described the basic pathology of the early lesion of syphilis, the papule. Unfortunately, there is another reaction which occurs later on in the disease between the spirochetes on the one hand and the cells of the tissues on the other, a distinctly different biologic reaction from that in the formation of the earlier lesions.

At what period or time after infection this obvious biologic change occurs varies in individual instances. It may occur in the first months of infection or be delayed for some years. This biologic reaction is very similar to Koch's phenomenon and is probably an anaphylactic reaction, or, in other words, the tissues are biologically changed in relation to the spirochetes through sensitization or are in a state of allergie.

This can be seen when one studies the histopathology of the late lesion of syphilis called the gumma. Here we have a more or less rapid reaction of cell formation to comparatively few organisms. It is an extended or exaggerated papule, formed of plasma cells, connective tissue cells, lymphoid cells, and numerous giant cells with marked obliteration of the vessels and with no particular tendency toward involution, therefore a large mass of cells is comparatively quickly formed in the dermal or subdermal tissues which, going in the course of least resistance, form a large neoplasm seen upon the skin as a hard red tumor formation. Necrosis and degenerative changes soon attack the center of the lesion, producing softening which extends to the cutaneous surface, breaks through, and may cause an ulcer, the depth of which depends upon the depth at which the process started and the severity of the local reaction.

In this instance the spirochetes do not meet with as much resistance as in the early stages and they extend their process peripherally, this in some instances causing serpiginous ulceration. The late lesions therefore leave scars due to the lack of power of reorganization on the part of the great mass of new formed cells. The late lesions of syphilis are usually asymmetrical as the localization of the spirochetes in any given site is generally due to trauma at that site. In this period of the disease the spirochetes can be demonstrated in the blood stream. At the points of trauma, either of mechanical or physical nature externally or a pathologic nature from within, the gummata are first formed.

CUTANEOUS MANIFESTATIONS

In the early stages of the disease, there are certain characteristic and diagnostic appearances which are common to all of the cutaneous manifestations, due to the location of the lesions and the peculiar distribution through the terminal vessels.

Color.—The color is usually described as of a coppery or “raw

ham'' tint, due to the peculiar consistency of the plasoma or the plasma cells of which it is composed.

Configuration.—The lesions have a tendency to be disposed in circles or segment of circles; in other words, grouped, due to the distribution of the emboli in the terminal arterioles and capillaries.

Polymorphism.—The lesions come usually in crops, one crop following closely upon another, due either to a later awakening there than at other points or to a late arrival of the organisms at these points. On this account, they are therefore in various stages of evolution and involution, the differences in their appearance depending on the stage of their formation.

Induration.—All syphilitic lesions, with the exception of the early macule, are hard and infiltrated, due to the fact that they are composed of new cell formations or are granulomata and all are situated superficially or deep in the derma.

Extension.—The early or late lesions when they coalesce to form plaques or conglomerations of lesions extend at the border in a serpiginous manner. They may extend more rapidly in one direction than in others, forming scalloped or serpiginous outlines. This peculiarity is due to the formation of new foci of infection at the edges of the existing lesions and when less resistance is met in one direction than in others, the process will extend more rapidly and continuously in that direction. As the lesions of the late gummatous type extend peripherally there is often a crusting and cicatrization in the center—a characteristic of all infective granulomata. The various peculiar and characteristic appearances of syphilitic lesions are always due to definite chemical or physical forces. The centrifugal or serpiginous extension of the lesions is due to the physical fact that the return lymph flow in the center of a lesion, when large and deeply formed in the cutis, is obstructed by coagulation and obliteration of the lymph and vascular channels, forcing the return lymph flow outward in several or all directions, carrying with it the virile spirochetes. Therefore as they pass outward in a more or less horizontal or lateral manner, they land in virgin soil to proliferate and form new foci, thus extending the lesion.

Symmetry.—The symmetry of early lesions is due to the general distribution; lack of symmetry in late lesions is due to the localization of the virus by various forms of trauma or other changes in local vessels or the reawakening of old foci *in situ*.

Absence of Pain or Itching.—In the early lesions which are uncomplicated, pain and itching are rare. It is almost an axiom that vesicular syphilides are the only type that itch. Pain may be experienced in the gummata, especially when adjacent tissues are involved.

Location.—The early eruptions tend to locate about the face, particularly about the forehead, mouth, and nostrils, the front of the trunk, and sometimes the back, the flexor surfaces of the extremities, and the palms and soles. These are the sites of predilection, but the eruption may be almost universally distributed or atypically distributed with wide areas of healthy skin between. The late squamous and the gummatous lesions are most frequently found about the points of trauma,—the knees, elbows, lower leg, shoulders, and nose, and are often associated in certain locations with professions or trades, as in the case of palmar lesions.

CLASSIFICATIONS

Classifications of skin lesions in syphilis have been made by many writers from as many viewpoints; some have divided the lesions according to the stages of the disease which, as has often been shown, are purely arbitrary periods with no definite time limits or sequence. Others have attempted to use for the basis of their division, the destructiveness of the lesions. What seems to be the best classification is that which is made according to the anatomical forms of the lesions, employing the fundamental types for description, and the terms "early" and "late" for the main divisions. Even this means of dividing the lesions into classes must be governed in its consideration by the fact that syphilis is of a most wanton nature and there may exist any variation or combination of the fundamental types and any variance in the time of their appearance.

Upon such a basis, and with its limitations fully in mind, the following classification is made:

Early
 Macular
 Maculopapular
 Papular
 Miliary
 Lenticular
 Papulosquamous
 Moist papular
 Varicelliform and varioliform

Late
Pustular—acneform
Ulcerative
Impetigo-form
Ecthymiform
Rupial
Tubercular and gummatous
Pigmentary and purpuric

The Macular Syphilide.—The macular syphilide, or syphilitic roseola, is by far the earliest and one of the most common of the cutaneous manifestations and frequently furnishes the deciding point in the questionable diagnosis of a chancre. It is the first visible sign of a general systemic involvement. While being the most universally constant of the various eruptive forms, its presence is often overlooked because of the fact that it usually occurs only on the covered portions of the body and has no subjective symptoms to attract attention to it. The average time of appearance is forty-five days after the appearance of the chancre or seventy days after the exposure, but it may follow the chancre in a very short time, it may recur, and it may be lacking altogether.

The macules first appear, in most cases, in the region of the epigastrium and then involve the entire chest and abdomen, the neck, and the flexor surfaces of the extremities, in the form of ill-defined, rounded or oval, hyperemic spots, rarely elevated above the surface of the surrounding skin. The color is a bright rose-pink, fading on pressure, but as they grow older, the color is less easily effaced and, on disappearing, either with or without treatment, a pigment spot is frequently left for some time.

The eruption is most frequently taken for the roseola of measles but the initial appearance of the latter on the forehead and the presence of Koplik's spots and symptoms of an acute rhinitis, should settle the point. Scarlet fever, with its "strawberry" tongue and high fever, should offer little difficulty. Drug eruptions, especially copaiba, may be suspected, but the history of such medication and the prompt disappearance on removal of the drug will rule out syphilis. As the color changes to a darker hue one might think of tinea versicolor but this disease is decidedly follicular and the microscopic examination of scrapings will reveal the *Microsporon furfur*.

The *maculopapular syphilide* is merely a transition stage from macule to papule. The macules become erythematous bases for small papular eminences variously disposed over the old macular sites. With

the elevation and the consequent stretching of the epidermis, there may be found a fine "collarette" scale about each papule. The distribution is more general and the tendency of all syphilitic lesions to assume annular or arcuate formations is usually followed here.

The Papular Syphilide.—As has been said before, the fundamental lesion of syphilis is the papule and it may therefore be found to present wider variations than any of the other main types. It may appear coincidentally with the macule as an example of the general law of multiformity in lesions of this disease, it may recur, it may be lacking, and in time limits is most variable of all, in some cases merging into the late tubercular form.

In distribution the papules are most generous and in certain localities they tend to become massed—along the hairline on the brow, forming the "corona veneris," beneath the mammary glands, and in the natural folds of the body. Their location alters their characteristics, the lesions being dry and scaly on the trunk, seborrheiform on the scalp, moist in the folds where the sweat glands are numerous, and hard and scaly in the palms and on the soles.

The Miliary Form.—This form of papular syphilide is very seldom met with, but when found seems to be more common in the female and is very rapid in appearance and spread. It is essentially follicular and chooses the sites of predilection for seborrhea,—the face, neck, shoulders, and sternal region. The papules are sharply limited, small but prominent, and situated on an erythematous base. The size is subject to marked variations, the average being that of a pin-head. At first bright red in color, it soon changes to a brownish red and leaves a dark stain when the papule has involuted. In the early stage, each papule may be surmounted by a vesicle and it is here that one finds the only itching that occurs in purely syphilitic lesions. The collarette scale is scanty. Annular configuration due to central involution of the papule is the rule.

From punctate psoriasis the differential diagnosis is made from the difference in location and the existence of larger flaky, mica-like scales in psoriasis, which when removed forcibly, disclose minute hemorrhagic spots. Lichen scrofulosorum occurs chiefly in childhood and the eruption is usually limited to the trunk. In early lichen planus, the larger, more pruritic, and violaceous character of the lesions should not offer much difficulty.

The Lenticular Type.—This is the most common of all the types

of papular syphilide and the most extensive in its involvement although not so rapid in its spread as the miliary type. The papules are sharply defined, very slightly elevated, more or less flat-topped, and roughly circular in outline. Here one sees the coppery color and the collarette scale more clearly than in any other form. While the entire skin surface may be involved, the sites of predilection are the forehead, shoulders, forearms, palms, and sacral region. Along the hairline on the brow, the corona veneris is often seen. Extension is slow and is accomplished by the appearance of new spots rather than by the coalescence of those already present.

In passing, mention might be made of two variations of this type, the nummular, or large flat papule, and the corymbose type, where small papules are grouped about a larger one in a satellite arrangement. The nummular type consists fundamentally of the central healing of the lenticular papule coincident with a peripheral spread, forming large coin-shaped lesions which have the usual characteristics of lesions of this stage.

The Papulosquamous Form.—Contrary to the usual scanty scale in other papular forms, there occurs now and then a profuse piling up of scales on the surfaces of the papules to such an extent that the term "psoriatic" syphilide has been employed by many writers. This excessive scale formation is due to certain physical causes, chiefly regional, and according to some writers there is an underlying individual idiosyncrasy in patients who would exhibit excess scaling in any cutaneous disturbance.

The chief location of the lesions of this type is the palms and soles. The epidermis in these places being thick, resistant to all disturbing factors, and closely adherent to the fascia beneath, imparts to the lesions a flattened appearance with little elevation, the growth being in the lines of least resistance, that is, laterally. Trauma in the pursuit of the patient's occupation usually precedes their appearance. The lesions begin in the center of the palm as dull red or flesh-colored spots about the size of a split pea. Serpiginous extension is the rule and the entire palm may be involved with central healing of the process and a limitation of the peripheral extension to the palmar surface of the hand, although it may encroach upon the fingers and involve their lateral surfaces. The individual lesions may be plucked out *en toto* by the patient and leave a small pit with punched out edges. The epidermis over the papules is gradually

lifted up and presents a dirty white lamellated scale with bright red spots in the exposed cutis. The process may consist ultimately of one large single lesion with healed center and papular border or it may consist of several arcuate formations of several papules each, or there may even be only a few discrete papules.

The diagnosis usually rests between palmar eczema, the so-called "trade eczema" of bricklayers, etc., and syphilis. In the palmar syphilide, there is no itching, the infiltration and border are well defined, and there is no history of previous moisture or discharge.

The Moist Papule.—When the epithelial covering of the papule is lost and there is a moist secreting surface left, the term "moist papule" is applied to the lesion. Perhaps the most important point in regard to this lesion is its extremely contagious nature.

The loss of the covering of the papule is favored by thin fine skin in areas where perspiration is constantly excreted. Therefore the lesion is found in the natural folds of the body, especially about the anal and genital orifices but also beneath the breasts, in the axillæ, the interdigital spaces, and the naso-labial folds. It is more common in the female. The location of the lesion, that is, the amount of pressure exerted there, has much to do with its subsequent shape, and while it is most commonly a variation of the papule, it may be the end result of any of the early lesions of syphilis.

It begins ordinarily as a flat-topped papule, roughly circular in outline, discrete for but a short time as adjacent lesions rapidly coalesce, and about one fourth of an inch in diameter. The covering, when bathed in perspiration, soon becomes macerated and is detached by friction of the contiguous parts. There is a marked tendency toward the formation of vegetating lesions by the hyperplasia of the papillary body and the resulting flat-topped lesion is known as the broad condyloma, or condyloma lata, in contradistinction to the acuminate, or peaked-topped, condyloma of gonorrhea. These condylomata of syphilis are not purely syphilitic in their entirety as the physical conditions of the part have a decided influence on the formation of the enormous cauliflower, deeply-fissured growths which are often seen in the genito-anal region.

Depending upon the amount of perspiration, the obesity of the patient, and the location of the lesions, they may have dry crusted borders, but the central portion is fundamentally a soft, flesh-colored plaque with a moist secreting surface.

The nature of the lesion with its top as broad as its base, or nearly so, is the distinguishing feature in differentiating it from the pedunculated vegetation of a Neisser infection.

The Varicelliform and Varioliform Syphilide.—Possibly because of improved hygiene and methods of treatment, there seems to be a decrease in the prevalence of pustular syphilides of the early stages, but in certain individuals whose skin is a favorable soil for any pyoderma, the condition is occasionally met with. Those with a superficial involvement belong to the early class of lesions, the deeper lesions being classed among the gummata.

The lesion is a small dark red papule at first with the rapid formation of a fluid exudate which soon becomes purulent. The epidermis then becomes depressed over the center of the papule from partial absorption of the exudate, the contents of the pustule dry, and a greenish black crust covers the lesion until this falls off and leaves brownish depressed scars which persist for some time. The sites of predilection are the forehead, the sides of the trunk, and the flexor surfaces.

Although the vesicular period of these lesions is very short, one may see them in sufficient quantities to suspect varicella, especially when polymorphism is absent as it may be in either disease. Furthermore, the transition in syphilis is much slower, the fever that ushers in varicella is greater, and there are more pronounced signs of inflammation.

In variola, the lesions are quite similar and yet the marked premonitory symptoms of variola, together with the absence of other signs of syphilis and the rapid transition through the different stages, render the diagnosis quite certain until the question of time eliminates what doubt may remain.

LATE SYPHILIDES

The Acneform Type.—This pustular type is quite generally acknowledged to belong to the later lesions. Located on the seborrheic regions, and follicular in character, the usual picture is that of numerous conical papular projections quite discrete, each surmounted by a minute pustule at its apex, and soon becoming crusted. The apical location of the pustule rarely leads to scar formation and involution is followed by a slight stain.

Aene vulgaris may be confused with this type, but the relation to

the period of puberty, the presence of comedones, the absence of febrile symptoms, and the appearance of lesions singly with the marked chronicity of acne vulgaris should rule it out. The same features apply to iodide and bromide acne, augmented by the history of such medication. Scabies should offer little difficulty.

The Impetigo-form Type.—As the name implies, the lesions of this type resemble impetigo contagiosa very closely and are fundamentally small, superficial pustules arranged in a group and surrounded by an areola. One may find discrete pustules, the individual lesions having a heavy greenish crust, the crusts being tenacious until the latter part of the eruption, when they fall off and leave coppery red pigmented spots, and sometimes, like the simple impetigo, whitish, persistent, disfiguring scars. The eruption involves the hairy regions in particular and may cause a permanent alopecia. From impetigo the differentiation is made by the indolent progress of the eruption and the early and persistent areola formation. Syccosis also involves the hairy regions but the lesions here are more furuncular, the alopecia only temporary, and the process much deeper. The scalp usually escapes in syccosis.

The Ecthymiform Type.—While practically the same as the preceding class, a separate division is made because this type of late syphilis is located chiefly upon the lower extremities and the pustule is much larger with a marked tendency for extensive destruction. Scarring is almost inevitable. Lowered resistance, such as in the cachectic, is a predisposing factor.

The Rupial Syphilide.—Perhaps no other lesion is more typical of syphilis than the rupial syphilide with its characteristic heavy, heaped up, "oyster shell" crusts, in spite of the fact that it is less commonly seen than some of the less typical ones. As with most pustular syphilides, the soil must be favorable and the subjects are usually suffering from malnutrition. The sites of predilection are the face, neck, and extremities.

Beginning with a discrete, flat pustule or bulla, formation of a purulent exudate is rapid, followed by rupture of the covering and a drying of the exudate in heavy crusts. Ulceration goes on beneath the crust and new crusts form from below as the ulceration extends peripherally, the new ones being larger than the ones preceding, till a conical greenish black mass of dried exudate gives the characteristic appearance with which no other disease than syphilis could scarcely

be confused. Scarring occurs here although the ulceration is rarely deep.

The Tubercular and Gummatous Syphilides.—These two forms of late lesions are classed together because the only difference in them is the depth of involvement of the tissues, both being the latest types of syphilitic skin lesions. In fact, one might say that a tubercular syphilide is a superficial gumma. They are usually few in number, asymmetrically disposed, and are most often found on the face, shoulders,—especially about the clavicle—the arms, thighs, and legs.

The tubercular type consists essentially of a small, superficial, circumscribed, solid tumor mass of a coppery color, varying in size from a pea to that of a bean. Where there is stasis, particularly in the legs, the color is deeper. Chronic in their course, they tend to become grouped in arcuate formations and undergo involution either by resolution or suppuration, leaving scars in most instances.

This type is generally found upon the face and the confluence and aggregation of nodules may impart a leprous appearance to the face, due to the accompanying thickening of the skin. Ulcerative termination of these lesions seems to depend upon trauma as the sites of predilection for the ulcerous tubercle are the areas most subjected to physical forces. Extension is a process of central necrosis, crust formation, and cicatricial healing, and peripheral formation of new tubercles along serpiginous outlines. On the trunk this serpiginous extension is oftentimes wide and destructive, especially in the malignant type. The elbow is another common site, due to repeated trauma in this location.

Rhinoscleroma, lupus vulgaris, and epithelioma are most often confused with the tubercular syphilitic. The absence of other signs of syphilis and the history of trauma in the first disease, the absence of the apple jelly nodules in lupus, and the rolled pearly border of the epithelioma are the principal points of difference. In leprosy, one finds areas of anesthesia, a softer feel to the tumors, a slower evolution, and a confinement of the lesions to the face, backs of the hands, and forearms. Smears from the mucous membranes well back in the nose, will usually reveal numerous Hansen's bacilli under proper staining.

The *gumma* is distinctly a syphilitic lesion of the latest stages, involving the deeper structures first and the skin secondarily by ulceration. It assumes the shape most convenient to the nature of its

location, being spherical where the skin is loose, and flattened out where the bones lie close to the surface as on the cranium and over the tibiae. Trauma influences the localization of gummata and they are most often found on the forehead, the nose, elbows, knees, ankles, and clavicle.

The usual course of a gumma is as follows: beginning as a pinkish oval tumor, painless, very hard, and rising but slightly above the surface of the skin, which is freely movable over it, because of its deep situation, it gradually increases in size, becomes softer in the center with a rubbery feel and some fluctuation, and the overlying skin becomes darker and begins to desquamate. The central portion breaks down and a large indolent ulcer is formed with sharply punched-out edges, a dirty necrotic base, sharply circumscribed, and quite painless. Extensive destruction may follow or the base may clear up, granulation tissue form, and healing occur, in time, with a kidney-shaped scar, pigmented about the border, to mark the site of the gumma. This scar is quite characteristic in itself.

The clinical picture is frequently sufficient for a diagnosis between gummata and the lesions of other diseases, but the time honored response, or lack of response, to treatment is of invaluable aid to the untrained. From epithelioma of the nose, the differentiation is usually simple from the rolled pearly border, the age of the patient, and the tendency of epitheliomata to bleed easily. Leg ulcers are many and varied, but the closest resemblance to a gummatous ulcer is the varicose type. Varicose ulcers have a sloping border, an irregular outline, and are located in most cases on the lower third of the leg and near the inside surface. There is almost always an associated edema, stasis, cyanosis, and of course, varicose veins. Gummatous ulcers are usually located on the upper third of the leg, although not necessarily limited to this region. The occurrence there is so frequent, however, that it might be said that 99 per cent of all ulcers near the knee, especially in women, are gummatous. The other diagnostic features of gummata have been mentioned above.

The Pigmentary Syphilide.—Following any syphilitic lesion there may be a loss or an increase of local pigment at the site of the former lesion. One of the most striking examples of this local loss of pigment is the "collar of pearls" or "leucoderma colli," the arrangement of leucodermic spots, seen best in brunettes, about the neck. This is believed by many to be pathognomonic of syphilis. Extensive

pigment formation may result that stimulates chloasma or tinea versicolor, but chloasma is usually in the female and on the face as well as the neck, while the pigment in tinea versicolor, on close inspection, can be seen to be on, and not in, the skin.

Hemorrhagic syphilide is merely a term applied to the complicating purpuric spots in some of the eruptive phases of the disease and is rarely, if ever, a sole lesion.

IV

THE REACTIONS OF BONES AND JOINTS

BY ALEXANDER EARLE HORWITZ, M.D.

TOO much emphasis can not be laid upon the fact that in syphilis as in any other disease, a diagnosis can and must be made by clinical signs and findings. Especially is this true in bone and joint syphilis, in which class of cases the laboratory findings are notoriously unreliable. Clinicians are unanimous in their statement that the Wassermann here is not to be relied upon as a strong factor in diagnosis.

In bone lesions of undisputed luetic origin, the Wassermann is a confirmative factor in less than 50 per cent. This is an undisputed fact. Why these negative findings should be so great in bone lesions as contrasted to those found in lesions of soft parts is unexplained, and no attempt will here be made to give reasons. With this fact in mind our attention and energy should be the more strongly directed toward signs and findings of a clinical nature.

To lay too much stress upon the confirmative test is an injustice to both clinician and patient. To say that a lesion must be luetic because the Wassermann is positive is as false as to say that it is not luetic because this test is negative. All lesions found in a syphilitic are not of syphilitic origin. They may be, but need not be. A syphilitic may harbor other diseases as well as one who is not syphilitic.

The clinical findings are ample and the confirmative test should be used as an adjunct much as the x-ray is used. Syphilis of the bones and joints may be divided into three classes:

- I. Congenital.
- II. Late hereditary.
- III. Acquired.

The findings in each of these three classes differ to a marked degree and are worthy of note.

I. Congenital.—Under this class will be included all cases where any sign of syphilis is noted either at birth or during the first year of life. Those of the osseous system are very often noted immediately at birth. Where the disease is advanced, fractures are seen at de-

livery or immediately after. These fractures are produced with but slight traumatism during deliveries not difficult and where ordinary fractures need not be expected. They are frequently overlooked for varying periods of time.

These fractures differ markedly from purely traumatic fractures. There is a pronounced weakness or even paralysis accompanying the disability. The pain upon manipulation is less. The joint distention (when the fracture is at the joint) is greater. Ecchymosis is slight or more often absent. Muscle spasm, a strong factor in traumatism, is entirely absent. Tenderness is pronounced not only at the site of fracture, but throughout the entire shaft. This picture is strengthened by other important findings easily seen.

A fracture at delivery or soon after, in cases where no fracture need be expected, calls for further examination. We will here find the following:

Weakness of limb both distal and proximal to fracture, out of proportion to usual disability. Thickening and tenderness of shaft at whose end the fracture has taken place. Tenderness and disability at opposite end of shaft. Should this involvement of the opposite epiphysis be absent, involvement, to a lesser degree, of the corresponding epiphysis of the opposite limb will be found. This symmetrical polyarthritis is very characteristic. The fracture is to be regarded as of spontaneous or pathologic character, requiring but slight or no violence.

The character of the joint involvement is, therefore, as follows:

Joint distention, polyarticular and symmetrical in distribution, asymmetrical in appearance. Bone thickening plus bone softening. Infiltration of capsule. Slight pain upon manipulation. Tenderness marked. Joint motion but slightly limited. Shaft involvement proximal to joint, gradually diminishing as we recede from joint. Weakness of limb, independent of fracture. Weakness more pronounced in upper limbs, less in lower. Suppuration may take place.

Favorite sites, in proportion to frequency, elbow, shoulder, fingers, knees, wrists, and ankle.

II. Late Hereditary.—Where symptoms appear between seven and twelve years of age, they are regarded as late hereditary. The findings here differ from those of the preceding class. Joint involvement is the exception, shaft involvement the rule. Here is noted the sabre tibia, a symmetrical spindle-shaped shaft, produced by succes-

sive layers of periosteum, tapering toward both extremities of the shaft. Tenderness is pronounced. Disability but slight.

Muscle Weakness.—Atrophy of muscles and tendons in lower extremity more frequently seen in this group. This permits of inversion or varus deformity. Where spasticities occur eversion or valgus is seen. There is no symmetry as to distribution in this class as in the congenital. Suppurations do not occur. Disability is progressive, but amenable to treatment.

III. Acquired.—No age limit is here set. The findings in the osseous system differ to a degree from the preceding two classes. We have here,

1. Synovitis.
2. Arthritis.
3. Osteomyelitis.
4. Periostitis.

1. Primary synovitis is frequent, with the following symptoms.

- (a) Marked distention of joint capsule.
- (b) Fluctuation and riding patella.
- (c) Slight tenderness.
- (d) Absence of disability.
- (e) Slight or no limitation of motion.
- (f) Slight pain.
- (g) No muscle spasm.

1. The important observation here is disproportion of joint distention to the pain and disability. The synovitis may be permanent or of the recurring type. This is usually not accompanied by shaft involvement.

2. *Arthritis.*—Primary arthritis is rare. It is usually an accompaniment of shaft involvement and is to be considered an extension of the process into the joint. Symptoms noted are:

- (a) Bone thickening. Synovial thickening and infiltration.
- (b) Marked tenderness.
- (c) Slight muscle spasm.
- (d) Moderate disability.
- (e) Partial limitation of motion.
- (f) Bone absorption.
- (g) Abscess.

Favorite sites: knee, spine, elbow.

The differential points in the spine from tuberculosis are the comparative freedom of spinal motions, the greater area involved, and tenderness of the palpable portions of the vertebræ. Paraplegia, while a possibility, has not been noted as a result of spondylitis. It may exist independently of it.

3. *Osteomyelitis*.—This begins as an ostitis, extending to the medulla. The symptoms are analogous to those of ordinary osteomyelitis with the exception that the proliferation of new bone is more extensive. The destructive process is slow and by direct extension. It is frequently limited to a small area. Pain is pronounced, abscess is frequent. Slight local and general rise of temperature. Onset never acute. History of trauma but seldom given.

4. *Periostitis*.—Not as frequently seen as in the late hereditary type. It may be a beginning of the osteomyelitis. It leads to bone proliferation in the shaft. Tenderness is marked. Subperiosteal abscess may occur.

SUMMARY

The points of importance are: The disease, where articular, is polyarticular, shaft involvement is seen in connection with it, joint function but slightly impaired, muscle spasm may be entirely absent, tenderness marked even in spinal involvement.

V

THE REACTIONS OF THE EAR, NOSE, AND THROAT

BY WILLIAM E. SAUER, M.D.

THE importance of syphilitic reactions in the upper air passages has long been recognized by all clinicians. The diagnosis is vital, not only as an aid in interpreting other symptoms and signs, but also because the disease here may be fraught with immediate danger to life, may result in permanent disfigurement, or grave interference with voice, respiration or deglutition. Further, early recognition of syphilis of the ear may spare the patient total deafness. That the disease is frequently manifested in the upper air passages is well known. According to Neumann syphilitic lesions occur as frequently in the pharynx as they do on the skin. Fischenbeck found, in a series of 235 cases, that the nose was involved 82 times, the pharynx 49 times, and nasopharynx 14 times. In the latter series, the disease could not be demonstrated in any other organ. Ballenger states that the larynx is involved in from 1 to 15 per cent of all cases of syphilis, the pharynx in 10 per cent and the nose in 3 per cent. Mauriac found the nose and pharynx involved 54 times in 237 cases of tertiary lues. The laboratory diagnosis of lues is undoubtedly a great aid, but that we can not entirely rely on laboratory findings in all cases, has been the experience of us all. The Wassermann reaction has proved the most valuable aid, but it should not be relied upon to the exclusion of clinical findings. It was hoped at one time that the diagnosis of initial lesions at least might be settled by finding the *Spirochete pallida*, but there are so many spirilla in the upper air passages that the general practitioner, and even the laboratory specialist, is not able to differentiate between them, so that ordinarily no reliance can be placed on examinations of the secretions coming from these parts. We should therefore, study our cases from every angle, and especially familiarize ourselves with the clinical manifestations.

Primary syphilis of the ear may occur on the auricle or in the external meatus, as the result of the use of infected towels and from the bites of individuals. The early lesions of the auricle or the meatus might readily be considered something indifferent. The history and the appearance must be carefully weighed. Granulation tissue, or polypi, or warts are frequently seen in the meatus, and

condylomata may be mistaken for them. Warts are more firm, granulation tissue less resisting to probe. Condylomata are paler than granulation tissue, and their bases of attachment are commonly much nearer the conchi than is the case with polypi. Tertiary lesions are to be seen here, as elsewhere, but usually not alone. Secondary and tertiary lesions may occur in the middle ear, and some cases of chronic suppurative otitis media are due to syphilis. Rapid destruction of the tissue of the middle ear, in patients not tuberculous, calls for a consideration of syphilis as a factor. Deafness is usually marked. Every middle ear condition in which there is a rapid loss of hearing with prolonged bone conduction should lead us to suspect lues.

Luetic involvement of the internal ear is not infrequent, occurring usually in the late secondary or early tertiary stages. Rarely it is seen in the early stages. The deafness occurring in later stages of syphilis are para-luetic lesions of the eighth nerve just as we find them in tabes.

The characteristic most to be emphasized is the suddenness of the deafness accompanied by tinnitus, vertigo, and loss of equilibrium. Both ears suffer as a rule, though often to a different degree. Sudden deafness, particularly in the adolescent, especially in the nonsuppurative ear is usually syphilitic.

Jones and Fischer have recently pointed out the value of the new labyrinth tests in making an early diagnosis of syphilis. For example: If a patient presents a suspicious initial lesion, and the ear test on the eighth or tenth day shows a nystagmus (after turning) of eighteen seconds, instead of the normal twenty-six seconds, syphilis may be suspected. If after three or four days more the nystagmus lasts only twelve to ten seconds, the diagnosis of syphilis is strongly suggested. Jones believes that in certain cases of syphilis of the nervous system, the involvement may be detected by an analysis of the eighth nerve, and its pathways, several years before it could be detected by any other method. The eighth nerve, owing to its extensive ramifications, and greater susceptibility to toxemia, he believes to be the most likely of all parts of the nervous system to be affected, at least to some extent, by the infection, and in advance of, or at least manifesting its involvement before the oculomotor, optic, or spinal nerves. These ear tests are not alone valuable in the diagnosis, but are also a help in estimating the efficiency of the treatment

in cerebrospinal syphilis; a progressive impairment in response to ear stimulation indicates a change for the worse; while on the other hand, a progressive improvement in response to the ear test suggests a change for the better. It is therefore very important that we be familiar with these reactions for there is evidence, according to Jones, both clinical and experimental to show that certain types of *Spirochete pallida* have a special affinity for the nervous system, and these cases are not so apt to have characteristic lesions either secondaries or tertiaries.

The prognosis of luetic involvement of the internal ear depends on the duration; in the early cases good, in the old cases absolutely bad. The salvarsan treatment is contraindicated in all cases of syphilis where there is any eighth nerve involvement, owing to the toxic action of the arsenic. Mercury and potassium iodide with pilocarpin give the best results.

NOSE

Primary lesions of the nose are comparatively rare. Buckley reported 95 primary lesions in 9058 cases, while four French observers report only 2 cases in 2244. Personally I can recall only 3 cases of chancre in the nose. Two of these were physicians, who had been infected through picking the nose with the fingers. A number of cases have been reported which resulted from improperly sterilized instruments. The hard chancre of the nose is usually flat and of moderate size. In the interior of the nose, especially on the septum, the chancre is usually slightly red or greenish in color, covered with pus, having the appearance of fungoid mass, but having the consistency of cartilage, and bleeds very easily. The surrounding mucous membrane is more or less inflamed and swollen. The nasal passage is obstructed and there is usually a bloody foul-smelling discharge. When the lesion involves the skin of the nasal vestibule, there may be more or less pain in the infraorbital region; in some cases there may be considerable headache. In some instances the submaxillary and the sublingual lymphatic glands may be enlarged. The diagnosis may at times be difficult, particularly in differentiating a primary lesion from malignant tumors which occur in this region. The diagnosis can not often be made until the secondaries appear.

SECONDARIES

According to Tissier, secondary lesions occur more frequently in the nose than is ordinarily admitted, owing to the fact that they are frequently overlooked both by the patient and the physician. The earliest manifestation is the so-called syphilitic catarrh, or specific coryza which may occur alone, or with a syphilitic pharyngitis, or laryngitis. This syphilitic coryza differs very little from an ordinary cold. In the former the process may be limited to one side, and the symptoms are not so stormy. Instead of a diffused redness there are only localized areas of erythema. The chief difference is in the duration of the process, the specific coryza lasting much longer. In children the so-called snuffles or coryza syphilitica neonatorum may be of considerable importance, owing to the interference with nasal breathing, and the resulting interference with the nourishment of the infant. To differentiate between an ordinary acute coryza and a specific rhinitis in a child is not always easy. If an acute rhinitis does not yield to ordinary treatment, lues should be suspected, and the child should be carefully examined for other signs of syphilis. The occurrence of papules or broad condylomata in the interior of the nose has been a disputed question. According to Schleich the papules are found most frequently on the septum, and on the floor of the nose. They often appear as milky white or grayish white epithelial thickenings, with an area of inflammation surrounding them. However, it is generally conceded that mucous patches occurring either alone or simultaneously with mucous patches in the mouth and on the fauces, are comparatively rare. Personally I do not recall having seen any secondary lesions in the interior of the nose.

Tertiary lesions of the nose are common occurrences. They occur in about 4 per cent of the cases and may appear from one to thirty years after the original infection. The tertiary lesions of hereditary syphilis usually occur shortly after birth or at the time of puberty. Gummatous infiltrations occur on the septum and turbinates. This infiltration is rarely observed clinically because patients do not present themselves for examination until the stage of softening and breaking down appears. Gummatous infiltrations involve the mucous membrane, cartilage, and bone. This infiltration may vary in size from a pea to a hazel nut. There is usually not a sharp outline, but a gradual fading into the normal tissue. Considerable time may elapse before there is a breaking down. This usually occurs in the

center of the infiltration, leaving finally an ulcer with a depth greater than its diameter. With the breaking down of a gummatous infiltration of the septum a perforation results, and with an extreme destruction of the bony support of the nose a sinking in occurs, leaving the well-known saddle nose. The subjective symptoms of tertiary syphilis of the nasal interior at the beginning may be quite indifferent, and are often mistaken for chronic coryza or a hay fever. After a time the discharge from the nose becomes more purulent, foul smelling, and bloody, with a loss of sense of smell, small crusts form in the nose which become difficult to expel; or the process continues, the foul odor becomes more apparent, and many observers consider the odor as a characteristic of syphilis. The pain in the nose and over the bridge of the nose may be quite severe at times. This pain may radiate to the ears and to the teeth. Frequently bony sequestra are blown from the nose, or may pass out through the nasopharynx. In the neglected cases extensive destruction may take place involving the bone of the entire septum, turbinates and hard palate. The diagnosis is usually easy but at times quite difficult. Any ulcer involving the bone and any sequestra at once point to syphilis. Perforations of the septum involving the bone portion are usually syphilitic. Lupus may destroy the cartilaginous portion but not the bone. A perforated septum involving the cartilage only may beluetie, but is usually due to a simple perforating ulcer. In tuberculosis the bone is not involved. All cases of ozena, and kindred nasal conditions or dystrophies should be subjected to a most critical examination. Of the deformities of the external nose, especially the saddle nose, very little need be said. It may be well to emphasize that not all saddle noses are due to syphilis. The same picture may occur following an abscess of the septum and following an injury.

The fauces, pharynx and nasopharynx are more often the seat of evidence in syphilis. In the fauces and pharynx we may have the initial lesion, the virus implanted frequently by use of infected instruments or finger; sometimes by perversion. First on the labii we may find an ulcer, pea size usually, indurated edges, surrounded by bluish white areola often with yellowish exudate, and situated on one side or the other of the median line, the so-called condylomata latum labii.

Within the oral cavity are seen, very frequently, the well-known mucous patches, which must be differentiated from ordinary stomat-

itic patches (ulcers) of the aphthous type, more frequent in children, but seen in adults.

Ulceration and irregular growths of the tongue, and tongue scars, are often syphilitic. Usually in neoplasms of the tongue of specific origin the growth (progress) is more rapid than in tuberculous or carcinomatous growths, especially in advanced age.

The faucial tonsils are involved frequently in syphilis, and the exudate, pseudomembrane, may be easily confused with diphtheria, Vincent's angina, and even thrush. The tonsils are usually swollen, reddened, have a patchy ulcer-exudate. The onset is more gradual than in diphtheria, the patient usually fever-free. In thrush we find the mycelium and the lesions are more discrete; and the buccal cavity generally involved; in Vincent's angina, the spirillum and the fusiform bacillus are found, but as both fusiform bacilli and spirilla may be found in a cover glass preparation from a tertiary ulcer, and according to Thomson, the Wassermann reaction may be present, apart from a concomitant syphilis, we are sometimes unable to reach conclusions at once.

Leptothrix should not easily be confounded with syphilis. The tenacious sand-like bodies, hard to dissolve, and the leptothrix mycelium will help out if necessary to resort to such examination.

All perforations of the palate, not traumatic, ulcers, especially deep ones with punched-out edges, and yellowish exudate; all cicatrices not otherwise accounted for, are usually syphilitic. We may have an initial lesion on the palate, a broad dark-red indurated papule; the secondaries occurring on the palate are usually erythematous or mucous patches, and they follow a symmetry as they do on the tonsils or pharyngeal wall. Tertiary lesions do not usually follow this symmetry, are more deeply ulcerative, or partake of a gummatous type, resembling granulation tissue, and involve the tonsil or soft palate by preference.

When we bear in mind that secondary syphilis frequently involves the pharynx, and that primary lesions are not infrequently situated on the tonsil, the importance of carefully considering the history and symptoms of every lesion not frankly a follicular tonsillitis, or pharyngitis, or peritonsillar abscess, becomes apparent. A marked glandular involvement, with an indurated swelling on the tonsil, especially unilateral, with or without fever, should at once arouse sus-

picion of a primary specific lesion. Enlargement of the glands tributary to the site is usually rapid, as well as marked.

Erythema, superficial ulcerations, mucous patches, usually of symmetrical distribution, swollen dull red tonsils, bluish red, symmetric, more or less crescentic patches on the soft palate at the base of the uvula, and sometimes a single mucous patch on or near the tip of the uvula, surrounded by a dusky redness; any one of these is often the first evidence of a specific secondary. Kidney-shaped ulcers on the tonsils are practically diagnostic of syphilis.

The gummata that may occur are from the size of a bean to that of a hickory nut or even larger. They may be diffuse or nodular, and occur anywhere in the pharynx and sometimes in the nasopharynx. Deep serpiginous ulcers may occur on the soft palate, tonsils, or posterior wall of the pharynx, and usually have a punched-out appearance, and are covered by a yellowish-gray mucopus.

THE LARYNX

Primary lesions of the larynx (epiglottis and ventricular bands) have been reported, but they are exceedingly rare. Secondaries are infrequent, though a perichondritis has occurred as early as 2½ months, while secondaries were manifested elsewhere. Tertiary lesions are common. Postmortem examination of syphilitic subjects reveals the larynx as involved in 15 per cent of the cases.

Condylomata or warts may be found as secondaries; they may ulcerate. Gummata are found in the tertiary stage; these may ulcerate.

The pain here is not so great as in faucial lesions, but if the ulcer is situated on the posterior wall of the larynx, dysphagia is apt to be a prominent symptom.

Induration about the ulcer may or may not be present; it is not as frequently so as in other localities. The ulcer has the characteristic punched-out appearance, there is little edema, and the mucous membrane is hyperemic and darkly congested. The cartilages may be involved, necrosed, suppurating, that is, there may be a chondritis. There may be a paralysis of both cords or only one. Stenosis may supervene, and call for intubation or tracheotomy.

The chief difficulty lies in differentiating syphilitic from tuberculous ulcerations, especially of the cords.

In general, it may be said the ulcerations of syphilis are deeper,

have more clearly defined borders, and are distinctly less painful than tuberculous ulcers.

The firm dusky appearance, irregular nodular aperture, involvement of the anterior half of the larynx, the raucous voice of syphilis, is in contrast with the pale infiltration, smooth aperture, usual involvement of the posterior wall, and weak voice of tuberculosis.

The hyperemic areas are not as intense and not as firm in tuberculosis, as in syphilis. There is in tuberculosis as a rule, involvement of the lungs, but it is not infrequent to see a syphilitic laryngitis in a tuberculous patient.

VI

THE REACTIONS OF THE OCULAR APPARATUS

WM. F. HARDY, M.D.

A SUBJECT dealing with a disease possessing the protean manifestations of ocular syphilis can not be adequately dealt with in a short paper such as is required in the present symposium. Only certain points can be touched upon and for the most part generalities indulged in. It is clearly understood that a syphilitic individual may suffer with any and every disease of the eye, which may be in no wise etiologically related to the lues. This is a truism which need hardly be stated, yet it is constantly overlooked or ignored. A syphilitic basis is often assumed rather than proved. On the other hand syphilis may be excluded from consideration because of negative physical or laboratory findings when in reality it is the causative agent. In the eye, time is the essence of treatment, as sight may be blotted out or compromised by reason of the delay in proper diagnosis.

The syphilitic reactions of the eye might be divided roughly into the inflammatory or direct and degenerative or indirect. The former subdivided into acute and chronic. Under acute inflammatory may be placed chancre, iridocyclitis, chorioiditis, optic neuritis, etc. Under chronic inflammatory, parenchymatous keratitis, chronic iridocyclitis and chronic chorioretinitis. The degenerative changes are chronic and include optic atrophy, paralyses of extra and intra-ocular muscles, Argyll Robertson pupil, etc.

Syphilis causes about 2 per cent of all eye diseases (Knapp). A careful study of the possible role of syphilis in producing ocular disease and particularly blindness, was made by Drs. J. W. Charles and H. D. Lamb at the Missouri School for the Blind. Wassermann tests were made in every case where consent could be obtained with the result that of 112 Wassermann tests, 11 were positive besides 5 cases of undoubted syphilis which had already received treatment and were negative: 16 cases of syphilis in 112 pupils, or 14+ per cent.

Syphilis is no respecter of persons, organs, or tissues. Its blighting effects may be felt by an eye before that eye has ever seen the light of day. The mesoblast which forms the greater part of the eye and particularly the more vascular part, is the tissue which bears the brunt of the luetic attack. The uveal affections (i.e., of the chorioid,

ciliary body and iris) constitute 43.2 per cent of syphilitic ocular lesions. Hereditary lues may produce a prenatal iritis chorioiditis or other affection leaving the eyesight in a sadly deteriorated condition. The congenital syphilitic influence is readily proved in parenchymatous (interstitial) keratitis: the absence of confirmatory evidence, in the way of other stigmata, being rarely noted.

A consideration of the ocular reactions from inherited syphilis is of paramount interest. Such a study has been completed recently by Dr. John Green, Jr., but is as yet unpublished. His observations are of a dependable value, since the survey of the subject was controlled throughout by the Wassermann test. Of the 100 children studied, every one had a definite lues with at least a ++ Wassermann. Fully 50 per cent showed undoubted eye lesions. The figures do not support Heine's contention that 80 per cent of syphilitic children show an optic neuritis. But one tenth that percentage was found. Few showed evidence of a present or past iritis, the characteristic changes being for the most part confined to the fundus. None of the tissues may, however, escape the blight of inherited lues. In children a secondary optic atrophy is not uncommon; a primary one must be exceedingly rare.

Despite the great prevalence of syphilis, direct infection of the eye or its appendages is uncommon. When occurring, such a lesion should be diagnosticated and treated early to obviate the disfiguring effects of scarring resulting from ulceration of the lesion. Because of their rarity these indurations may be readily overlooked. Physicians have suffered this mode of infection in quite a number of instances. The spitting and coughing of a patient whose throat is being examined, is the usual manner of inoculation. De Schweinitz' case was unique in that the physician was infected by some uterine fluid during the delivery of a child. Among the laity the lid or conjunctiva is primarily infected, sometimes the result of the filthy method of removing a foreign body from the eye with the tongue, a custom prevalent in Russia. Spratt cites the fact that Bulkley tabulated 9058 cases of extragenital chancre, 372 of which were of the lids or conjunctiva. Spratt personally observed a chancre of the bulbar conjunctiva situated at the limbus. He was able to find a record of but 21 cases of bulbar chancre up to 1913 and of these only three were at the limbus. Dr. Richard Weiss and I have one to report at a later date. Extragenital chancres affect the eye in 3 to 5 per cent of cases.

The lids are the usual site and are most frequently affected at the mucocutaneous junction. A chancre of the eye retains its characteristics of button-like hardness, definite limitation, central ulceration and regional gland swelling. A primary lesion of an eye is thought by some to render that eye prone to subsequent syphilitic manifestations. The eye may also be the seat of secondary and tertiary lesions. A characteristic of papules (secondary lesions) is that they are usually multiple, whereas gummata are generally solitary. The iris and conjunctiva show papules. The iris, sclera, ciliary body, lids, tarsus, choroid and rarely the optic nerve show gummata. The syphilitic papule of the conjunctiva may resemble phlyctenular disease. A gumma of the lid might conceivably be confused with a chalazion.

Primary syphilitic affections of the lacrimal apparatus are infrequent. Syphilitic disease of the lacrimal gland is unilateral, showing itself as a painless tumor and occurs in the secondary or tertiary stage. Secondary effects are not unusual, an instance being the blennorrhea of the lacrimal sac associated with "saddle nose." Changes in the bony lacrimal canal may often give rise to a secondary epiphora and dacryocystitis.

Of late years so much dependence has been placed on the Wassermann test that the associated clinical findings in parenchymatous keratitis are overlooked. One must not disregard such obvious symptoms as Hutchinson's teeth, rhagades, tophi, enlarged lymphatic glands, arthritis and last, but by no means least, the occasionally associated deafness. Several points regarding this affection are worthy of mention. It is one of the latest forms by which hereditary lues manifests itself. A purulent condition does not occur and consequently ulceration of the cornea never takes place. Parenchymatous keratitis is a hereditary lesion, but 3 per cent of cases being due to acquired lues. It occurs usually between five and fifteen years of age and represents an attenuated syphilis of the mother. According to some authors among them Collins, a woman with inherited lues does not transmit the taint to her children. Schieck (ztsehr. f. Augeneheilkunde, xxxii p. 95) has tried to explain parenchymatous keratitis on the basis of anaphylaxis holding that the theory of direct toxic effect is insufficient. The onset of the affection following a trauma occasionally occurs and constitutes an important medicolegal question. Knapp (Med. Ophth.) states that the connection is still undecided. Arguing in the affirmative is the record of a patient with lues and cata-

tract operated upon by me last spring, who developed an interstitial keratitis in the eye operated upon, several weeks after the extraction. This brings up for consideration the ill effects often obtained after a faultlessly performed operation on the eye. The lighting up of a plastic iridocyclitis after cataract extraction may sometimes find its explanation in a latent and unrecognized lues.

Ocular syphilis is represented by paralysis of the ocular nerves in 18 per cent of the cases. The 3rd, 6th, 4th, 7th and 5th are affected, the frequency being in the order named. External ophthalmoplegia is much more frequent than internal. Ptosis and isolated paralyses are often, but not always, due to lues. Nystagmus is secondary to brain or cord lesions. Involvement of the muscles is a late symptom in lues. Disturbances of the accommodation and of the pupil are common. A unilateral Argyll Robertson pupil is rare and is generally the forerunner of general paralysis. The seat of the lesion in the Argyll Robertson pupil has been the subject of much discussion. Some of the more recent observers look upon the ciliary ganglion as the affected part. The immobility of the pupil to the light reflex can precede a metasymphilitic disease for several years and can be during that time the only sign of syphilitic infection (Lutz). Paralysis of accommodation often unilateral, is frequently combined with paralysis of the pupil. It is an evidence of tabes, brain syphilis and progressive paresis. Chronic ophthalmoplegia and ophthalmoplegia interna are commonly the result of cerebral syphilis and also occur in tabes and paresis. The theory that different strains of spirochetes exist some having a special affinity for nervous tissues receives some corroboration in the family (reported by Grossman (Jour. Am. Med. Assn., lxvii, 963) affected with paralysis of the sphincter pupillæ and ciliary muscle.

Symphilitic inflammation of the iris may occur any time between intrauterine life and senile death. The most typical cases are those seen contemporaneous with the secondaries in which instances the nodules noted on the iris may be compared to papules or condylomata. Late in lues, iris nodules may appear and must then be considered as true gummata. The majority of cases of iritis occur within one year after infection. As the ciliary body is closely allied to the iris embryologically it participates in varying degrees in all inflammations of the iris. This iridocyclitis must be looked upon as one of the commonest ocular reactions of syphilis. Syphilis was formerly considered

the causative factor in fully 50 per cent of the cases of iritis, and while it is yet accorded the dominant role, a lower percentage, probably 30 per cent, must be accredited it. Iritis affects both eyes in one-fourth of the cases. Relapses are common. Complications such as chorioiditis, cyclitis, retinitis, optic neuritis and keratitis occur in one-third of the cases. Secondary results are glaucoma, cataract and detachment of the retina. Iritis apart from interstitial keratitis is rarely found in inherited lues. Papules of the iris are usually multiple and at the pupillary border. Gumma is rare, solitary, and affects the ciliary body or occurs at the ciliary border of the iris. It is thought by many that a frank outbreak of syphilis cutaneous and iritic, is seldom followed by cerebrospinal manifestations. Whether this is fictitious or not, it is remarkable how seldom paretics and tabetics give evidence of a precedent iritis.

The sclera may rarely evidence a scleritis or a gumma which latter is often solitary but sometime multiple and situated usually in the upper temporal quadrant. It is well defined and painless. Tertiary syphilitic periostitis rarely attacks the orbit. Exophthalmus and paralysis of the motor and sensory nerves result from a process at the apex of the orbit.

Lesions of the chorioid are almost inseparable from those of the retina, hence the term chorioretinitis is used. The pathology of the two tissues may be considered together. Chorioidal lesions occur in the late secondary and early tertiary stages. They may be solitary, few in number, or numerous and widely disseminated. Exudative chorioiditis is frequently the result of either acquired or hereditary lues and consequently may be observed at any age. Syphilitic retinitis is a common result of acquired lues. It is usually associated with disease of the uveal tract particularly the chorioid. Primary syphilitic retinitis is uncommon. A long-continued chorioretinitis results in optic atrophy and the pigment layer of the retina suffers to a great extent. Lues may produce a chorioretinitis which simulates retinitis pigmentosa. At times syphilitic disease of the retinal vessels produces a retinitis of a hemorrhagic variety, but the retinal vessels may show changes the result of syphilis independent of a retinitis. About 24 per cent of all cases of optic neuritis are due to syphilis. The neuritis is primary, the optic atrophy is secondary. A primary syphilitic optic atrophy does not occur. The neuritis appears as a simple neuritis or as a retrobulbar neuritis. Syphilitic optic neuritis results

either from a direct implication of the nerve or indirectly the result of inflammations or gummata within the cranial cavity. Gumma of the nerve is a rare condition.

Syphilis is more disseminated now than ever before and the optic nerve and retinochorioidal lesions are alarmingly frequent. Abadie (*Ann. D'Ocul.*, cliv, p. 734) attributes this to an increased virulence of the spirochete due to its rapid passage through many individuals. This he thinks can be abated only by attention to two points: (1) the mode of administration of mercury and (2) persistence and continuity of treatment.

In conclusion it may be stated that probably more people seek the services of the ophthalmologist for headache than for any other one symptom. Careful refraction and ocular examination may fail to give relief. Syphilis in such cases should not be lost sight of as a possible cause.

DISCUSSION

Dr. John Green.—In the few words which I have to say on this subject, I shall confine myself to ocular involvement in hereditary syphilis. It has long been recognized that the eyes are frequently compromised in the hereditary form of the disease. Thus Rabl found, in 127 cases, ocular involvement in 39 per cent, Fournier in 212 cases, found ocular involvement in 48 per cent. It is stated by Ohanian that 0.5 per cent of all ocular diseases are caused by hereditary syphilis.

As a rule ocular lues appears a few weeks after birth, due to the fact, as stated by Igersheimer, that the infection occurs in the later months of intrauterine life.

Every tissue of the eyelids and eyeballs may be affected. Interstitial keratitis is the most frequent ocular complication; it occurs as a manifestation of late hereditary syphilis. In 2000 cases it occurred in nearly 50 per cent. Diffuse clouding of the vitreous leading to greatly diminished vision, is sometimes encountered in infants and children. This, according to Sydney Stephenson, a distinguished British Ophthalmologist, points unmistakably to syphilis.

My study, to which Dr. Hardy has alluded, concerns the eyes of 100 syphilitic children from the pediatric service of the St. Louis Children's Hospital. No child was admitted to the series, in whom the clinical diagnosis was not confirmed by a positive Wassermann. Forty-eight of these children had spinal fluid Wassermans made, of which 16 were positive and 32 were negative. Seventy-four of these 100 children showed unmistakable ocular signs of hereditary syphilis. The following abnormalities were observed: Anomalies in the size and reaction of the pupils, concomitant and paralytic squint, ptosis, nystagmus, keratitis, iritis, posterior polar cataract, vitreous haze,

several varieties of retinochorioiditis, perivascularitis, optic neuritis and optic atrophy.

The most constant eyeground picture and one which I believe to be characteristic of hereditary syphilis was observed in 28 cases. Tiny dots of brown or brown-black pigment are strewn fairly evenly over the retina. Sometimes the entire fundus is peppered, more frequently the distribution is confined to large peripheral areas. The individual dots are round, of irregular outline and vary somewhat in size.

This picture must be differentiated from the gray punctation seen in many blond fundi, but this is a matter of no difficulty after a few of the syphilitic type have become impressed on the mind.

As a result of this study I am convinced that no physical examination of a syphilitic child is complete without an eye examination which shall include a careful search of the central and outlying portions of the eyeground. Unless such an examination is made the clinical picture will not be complete and data of value in prognosis and treatment will not have been ascertained.

VII

THE REACTION OF THE CARDIOVASCULAR APPARATUS

BY ELSWORTH S. SMITH, M.D.

AS TO the importance of this subject, Fordyce quoting Lenz says that in the large cities 25 per cent of syphilitics die of aortitis including angina pectoris, aortic insufficiency, and thoracic aneurysm as against 3 to 4 per cent of paresis and 10 per cent of luetic affections of all other viscera.

Brooks¹ based on 50 consecutive autopsies in syphilitic subjects finds that 66 per cent of luetic cases die with severe circulatory disease apparently of luetic origin.

Warthin from postmortem examination of 200 luetic subjects (50 congenital and 150 acquired) feels that syphilis is the most important etiologic cause of cardiac disease (endocarditis and myocarditis). He has also found spirochetes more often localized in heart than liver and has found these organisms in the heart, when nowhere else, confirming syphilis as essentially a vascular disease. In 41 postmortems he found spirochetes in the heart in 36 cases, in the aorta in 32 cases, and yet in all these 41 cases lues was denied or unsuspected in 25, clinically cured in 11 and clinically active in only 5.

As has been pointed out by other contributors to this symposium, the laboratory method of diagnosis of lues is not to be depended on, solely, by the practicing physician, for in the first place it is not always available particularly to those working at a distance from medical centers and secondly when available is not by any means always infallible, especially the negative evidence. And in this connection we wish to cite that in our Internal Medical clinic at the Washington University Medical School where a study of 2920 hospital and dispensary cases was undertaken at the suggestion of Dr. George Dock by Day and McNitt² to determine through routine Wassermann reactions the incidence of syphilis in different social classes of patients these observers collected in this study 51 cases in which the clinical diagnosis had been made of aortic regurgitation, thoracic aneurysm or angina pectoris but in which the Wassermann was positive in only 30 or 59 per cent while it was negative in 21 cases or 41 per cent speaking for the large percentage of cases in which the diagnosis of lues may be made in the face of a negative labora-

tory report. Then too, through the positive evidence of the laboratory, we only recognize the individual as the subject of lues, clinical methods of investigation being required to appreciate which of the different internal organs are involved in the luetic process and to what extent.

Familiarity with the incidence of a disease is of course of the greatest assistance in its clinical recognition.

We are all familiar with the importance of lues as an etiologic factor in chronic aortitis, aortic regurgitation, and thoracic aneurysm. Schultze, for instance, holds lues to be the cause of aortitis in practically all cases and Hempeln says a definitely diagnosed thoracic aneurysm means syphilis eight to twenty years previously. Etienne believed 70 per cent of aneurysms to be luetic. Forty-one per cent of cases of aortic regurgitation are of luetic origin, according to Pearce³ tabulating the cases reported by a number of authors. But we shall not detain you longer in the consideration of such well-recognized types of cardiovascular lues, but devote the remaining allotted time to some manifestations of the disease in the organs of circulation which have not, up to this time, been so generally appreciated. And at once we must call attention to the fact rather recently established through the studies of Brooks and others that from the changes in the heart originating as they do in and about the arteries, it must be evident that the involvement of the heart should come early, as we doubtless have in syphilis, as Brooks states, a septicemia or lymphemia.

Such usually irremediable luetic lesions therefore, as above alluded to, viz., chronic aortitis, aortic regurgitation and thoracic aneurysm are detected as a rule, only as late in the course of syphilis as from 15 to 20 years after the initial lesion still the involvement of the heart and aorta actually dates back to an early period in the so-called secondary stage of the malady. So engrossed, though, as a rule, are we physicians with the control of the skin, mouth, and lymphatic lesions, that we fail to realize the all important truth that lues in its early stages is an acute infectious disease and as such is just as prone as is rheumatic fever to attack the circulatory apparatus, yes, even more so, for syphilis is conceded to be a vascular disease *par excellence*.

Brooks in fact reports a case of lues in which death resulted unexpectedly before the secondary rash and before the diagnosis had

been made, from a minute perforation of the wall of the aorta just above the ring, the postmortem showing typical syphilis in myocardium, particularly involving the vas vasorum of the aorta. And so while the clinician would never for a minute have a case of rheumatic fever under observation without daily careful search for heart damage, this same clinician will probably assume the care of a case of syphilis without the possibility of the circulatory system being involved in secondary lues ever occurring to him, and as soon therefore as the more external manifestations of the malady have disappeared the cardiovascular lesions are allowed to proceed unrecognized to ultimately result in such incurable and fatal conditions as aortic regurgitation and thoracic aneurysm which might have been controlled by an appreciation of these lesions of the vascular apparatus at their incipency in the secondary stage and the institution of specific treatment, sufficiently intensive and prolonged to prevent irremediable damage. A warning that should be especially heeded by the syphilologist and genitourinary man unaccustomed as they are to view the syphilitic from the standpoint of the circulatory system, but who, as a rule, nevertheless see the majority of cases of early syphilis, for the internist and general practitioner are often guilty of the same serious error and that is a serious error, which permits of a possibly curable lesion eventuating in an incurable and fatal one.

But these early reactions of lues in the heart and aorta are recognizable if carefully observed and studied, when they will then be found to manifest precisely the same symptoms which at times accompany the febrile stage of most infections, such as typhoid, rheumatic fever, septicemia and the like.

Several cases seen in the early secondary stages by Brooks in Fordyce's service manifested such unmistakable evidences of myocardial disease as tachycardia, extrasystoles, and numerous other irregularities of tone rhythm and force, which when submitted to vigorous specific treatment showed within three days the disappearance of these signs, and all symptoms of cardiac disease vanished without resort to circulatory measures except rest in bed.

And Brooks goes on to say "now that the spirochetes of syphilis have been demonstrated in the heart muscles there remains no argument as to the specificity or significance of these lesions. It is inevitable that they should be followed (if not controlled) by changes

of a more or less permanent and often grave nature." Again Moore⁴ reports the case of a young man twenty-four years, with macular eruption over his body and a strongly positive Wassermann, complaining of precordial pain of a few days' duration and temperature of 99.6° and pulse of 110, slightly enlarged cardiac area of dulness, occasional extrasystoles and soft systolic murmur at base. Since receiving antiluetic treatment his cardiac symptoms have disappeared.

How vividly should reports of cases such as just quoted bring home to us our responsibilities in the appreciation of cardiovascular syphilis in its early stages that the later disastrous ravages of the disease may be prevented. Cardiovascular syphilis therefore should be appreciated as early as possible for the following two most important reasons: First, that through intensive specific treatment luetic involvement, to any extent, of the heart and arteries may be prevented. Secondly, that where the heart and aorta do become involved, then through this same intensive treatment to prevent the early cardiovascular lesions becoming the later incurable fatal maladies. On this point Brooks states that those cases in the active progressive periods of the secondary stage, which have been treated by modern methods, have thus far shown no recognizable cardiac complications, while where cardiac lesions or symptoms have appeared and vigorous methods of treatment been applied, disappearance of these signs and symptoms has followed in most cases, allowance, however, being made for the fact that a sufficient number of cases which received vigorous and protracted treatment in the early stages of the infection have not as yet remained long enough under observation to justify definite conclusions in this respect. Lydston⁵ calls attention to the danger of late complications in viscera affected with syphilis in the early stages. He believes it is never safe to depend on laboratory or clinical tests to prove a syphilitic cured, eternal vigilance and repeated periods of treatment are the only safeguards.

A second phase of lues of the circulatory system that is also not generally appreciated is chronic syphilitic myocarditis. As in the acute form of cardiac lues the most frequent symptoms of this condition are (1) arrhythmia, especially under strain, (2) associated frequently with heart murmurs or the accentuation of preexisting

ones; but the presence of these murmurs is in contrast to early cardiac involvement in which endocardial murmurs are rather rare, comparatively speaking. Brooks in an analysis of his postmortems states the presence of endocarditis in 74 per cent of the subjects, 14 per cent of aorta, none of mitral alone, but 34 per cent of aortic and mitral combined. (3) Precordial pain is also as frequent a symptom in the chronic as in the acute forms of the malady and partakes frequently of the character of angina pectoris. This pain is often nocturnal in character. (4) The history of the case may be in many cases misleading, first because many patients among the better classes, especially, conceal their infections, while among the lower classes the secondary lesions may have been overlooked for lack of intelligent observation. (5) When a history is obtainable the cardiac lesion has usually not been detected before about 15 years after the infection. (6) Dyspnea is also present especially with physical effort. (7) According to Fontana⁶ fever is very frequent, often for prolonged periods, with marked remissions resembling a septic fever or an atypical typhoid.

In the diagnosis of the chronic type we have not, as in the acute form of myocarditis, the presence of a known syphilitic to assist us, but with a thorough appreciation of the frequency of lues as a cause of chronic disease of the myocardium, recalling especially Cabot's statement that 12 per cent of failing hearts are due to lues, together with a careful history and physical examination, and above all having resort to one of the most valuable diagnostic aids, that of the therapeutic test, a correct diagnosis may be reached in the majority of cases. But what we wish to accentuate in this connection is that instead of never thinking of lues as a cause of chronic myocarditis, such a possibility should be our first thought and in doubtful cases we should give the patient the benefit of the doubt and administer specific treatment which, should the patient have chronic syphilitic myocarditis, will result in great benefit if not apparent cure of his trouble, while cardiac remedies alone would probably accomplish little or nothing. And finally, why should the therapeutic test in this class of cases appear any less scientific than in gumma of the brain for instance?

We must also constantly bear in mind that lues is a comparatively frequent cause of general arteriosclerosis, especially in subjects under

40 years of age, a fact that our attention has been called to by Pearce and Longcope, and as a corollary Stokes-Adams syndrome and heart block have been frequently reported as having been due to syphilitic disease, and several investigators record improvement in these conditions under modern methods of specific treatment. So also a not insignificant number of cases of angina pectoris have been ascribed to lues as their etiologic factor with likewise beneficial results with specific remedies. A few cases briefly presented may make more clear some of the above statements.

CASE 1.—B. W., Jr., white, male, forty-eight years, seen Dec. 29, 1914. Precordial pain radiating to lower border of left scapula, excited by slight exertion but present at night when quiet; dyspnea with at times suffocating spells. Physical examination: Double mitral lesion. Nocturnal pain suggested lues and history elicited. Chancre thirty years before. Wassermann was then made and reported 4-plus. Diagnosis, double mitral lesion and probably coronary sclerosis specific. Treatment, mercury and iodides. In bed at hospital six months and at home 18 months. Result: Jan. 1, 1919. Restoration to cardiac compensations, loss of anginal pain, has regained weight and strength, able to be out and about in comfort.

CASE 2.—A. B., white, male, age forty-three, seen Nov. 14, 1919. Dull pain under sternum for ten years always and only nocturnal which disturbs rest. Neisser infection in 1902. Denies lues. Physical examination: Periostitis of lower end of sternum and lower ribs. Systolic murmur at apex not transmitted: blowing systolic murmur over aortic area conveyed upwards into vessels. Clinical diagnosis: Lues of heart and sternum and ribs made before making of Wassermann which was 4-plus. Dec. 5, 1919, pains less, feels better since on specific treatment.

CASE 3.—O. R., female, thirty-six years of age, seen Nov. 22, 1919. Symptoms date back to October, 1918, following an attack of influenza. Has had pain and sense of weight under sternum, pains radiate to sides and back and are worse at night, interfering with sleep. Dyspnea on lifting a weight, going up stairs, or doing a great deal of walking. One miscarriage without apparent cause. History of nocturnal pain and miscarriage suggested lues. Wassermann then made, which was feebly positive. Physical examination of heart negative. Diagnosis mild angina pectoris of luetic origin. Placed

on Hg December 1, pain very much better, can now sleep at night, feels better generally.

CASE 4.—Mrs. K. T., thirty-nine years, seen December 2, 1914. Palpitation for several years, more marked lately, at times with attacks, has had pink foamy expectoration. Slight edema of ankles at times, attacks more marked about menstrual periods, patient very nervous, Articular rheumatism in 1904, Tonsillitis two years ago. Physical examination: Heart enlarged to left, presystolic mitral murmur, systolic shock. Because of mitral lesion with rheumatic and tonsillar history, lues was not at first looked for carefully. Later patient entered a hospital where routine Wassermann was found 4-plus and after specific treatment she reported on June 1, 1915, that she felt completely well and had no more heart symptoms.

CASE 5.—M. A., female, forty-seven, religious teacher, came under observation October 9, 1919. Influenza Feb. 11, 1919, and March 16 began to have anginal pains which culminated in several severe attacks of angina pectoris in which she experienced feeling of impending death. Physical examination: No cardiac enlargement, systolic murmur at apex not conferred into axilla. Because probably of her vocation lues not suspected. After placing her in hospital, the routine Wassermann was found to be 4-plus, and on further study of pain, patient stated that it was largely nocturnal. On specific treatment she is improving.

CONCLUSIONS

1. Cardiovascular lues develops primarily in the secondary stage of the disease.

2. The heart should be as carefully watched in the acute stage of syphilis as it should be in a case of acute rheumatic fever.

3. If the heart and vessels be so watched, the early cardiovascular lesions can be detected in the majority of cases and thereby the late fatal affections probably prevented through sufficiently intensive and prolonged treatment.

4. A sufficiently large percentage of cases of chronic myocarditis are of luetic origin to force the clinician to search carefully for syphilis in all such patients that they may enjoy the beneficial effects of specific treatment even in doubtful cases.

5. Syphilis probably plays a not insignificant role in the etiology

of arteriosclerosis and in the more rare affections as angina pectoris, heart block and Stokes-Adams syndrome.

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VIII

THE REACTIONS OF THE ALIMENTARY TRACT AND
EXTRAABDOMINAL VISCERA

BY R. WALTER MILLS, M.D.

SYPHILIS, a highly protean disease, may affect any portion of the alimentary tract or the extraalimentary abdominal viscera. While this fact is established, a knowledge of the subject has been slow of development and it is only within the past few years that a basis for a practical clinical conception of the condition has become established. The reasons for this are evident. Lues of the abdominal viscera is rare, consequently few have had the opportunity to study a sufficient material at first hand to reach conclusions. The difficulty of confirming findings and the indefiniteness of a good deal of the evidence offered in the literature cluttered by such handed down, illy confirmed, often palpably confused matter is apparent. Other factors make the subject difficult. The similarity in the physical findings and symptomatology of visceral lues and nonspecific conditions. The dependence on and unreliability of the therapeutic test alone, and the fact that many of the visceral lesions surely attributable to lues are late secondary results not macroscopically or histologically characteristic of syphilis. The amenability of syphilis to treatment has been an impediment to the acquisition of knowledge. Symptoms arise and are misunderstood. Other evident indications of syphilis are discovered, treatment is administered, the evident and the obscure condition disappear, leaving no clue as to the exact nature of the less well understood affection.

During the past few years two powerful aids have become available that have done much to clarify the situation and crystallize our knowledge of visceral syphilis—the Wassermann test and the x-ray. The serological test obviously as a method of direction and exclusion in a broad sense. The x-ray by affording direct evidence of the nature of the pathology and as a means of diagnostic elimination of other conditions now well recognized through its use. Other things that have advanced our knowledge of visceral lues are the better understanding of splenic, hepatic, pancreatic, and hematogenous disease; better knowledge of surgical pathology and the more general use of sigmoidoscope and esophagoscope.

In a consideration of visceral syphilis it is best to emphasize that the condition is rare; this with the possible exception of syphilis of the liver. On the other hand, instances when encountered present diagnostic and therapeutic problems of such practical importance as to make a general knowledge of the subject indispensable. Further there is a constantly growing impression that visceral lues like other expressions of syphilis is less rare than has been heretofore supposed.

It seems best in a presentation intended to be of general interest to give emphasis to conditions a knowledge of which has become reasonably exact rather than to others often of extreme rarity whose occurrence is less conclusively established. For the present it is best to hold as syphilitic only those visceral lesions capable of giving direct evidence either through actual visualization, appreciation by palpation or the x-ray. Such conditions are as remarked essentially tertiary.

Clinical visceral lues is essentially a late tertiary manifestation. Primary syphilis occurs only in the mouth, rectum and anus—in the latter instance usually as the result of unnatural practice, though in women anal chancre may be the result of contact in rare instances. Demonstrable secondary lesions occur in and about the mouth and by extension in the esophagus, also in the rectum. They are much quoted as occurring in the stomach as a gastritis or even eruptive lesion. The substantiation of this is not conclusive. Swelling of the spleen and some hepatic involvement as expressed by jaundice and hepatitis sometimes occur in the secondary stage.

Tertiary lesions may occur in the form of gumma, gummatous ulcer, gummatous cicatrix transitionally passing into resulting sclerosis, diffuse infiltrative, and secondary work hyperplasias as in the instance of the spleen in cases of syphilitic anemia, and finally as amyloid. The gummatous sclerotic and infiltrative types are those of clinical importance.

Syphilis is definitely known to affect all portions of the alimentary tract, and when there present, its manifestations fall into two groups as to their clinical significance. Uncomplicated essentially syphilitic lesions frankly amenable to specific treatment and consequently frequently unrecognized, or wanting the diagnosis of syphilis, mistaken for other conditions. In contradistinction, lesions resulting in stenosis, and such other infiltrative mutilation of the part as to cause the symptoms of motor incompetence to preponderate. It is these resultants of specific infection and especially their combination that

make the symptomatology of alimentary syphilis so imitative and variable.

The parts of the alimentary tract most frequently involved and of greatest clinical interest are the stomach and large intestine, probably always the distal colon. Syphilis of the esophagus and small intestine occur. The disease in the esophagus is rare and is generally unrecognized. When nonobstructive its results are not incapacitating and the lesion not characteristically luetic in esophagoscopic appearance on account of secondary infection. When stenotic the symptoms of obstruction predominate, the etiological factor being often lost sight of. The esophagoscope has been the means of chief enlightenment. Gumma ulcer and cicatrix occur. Mucous plaque as a secondary manifestation and esophagitis usually as a pharyngeal extension occur. During the terrible pandemic of fulminating syphilis late in the fifteenth century a frequent cause of death was starvation due to aphagia resulting from secondary esophageal syphilis. The chief practical lesson is that benign sharply localized esophageal stenosis coming on late in life especially if a history of transitory stenosis years previous is given and no history of caustic or foreign body traumatism is obtained, should be suspected as luetic. Aside from specific treatment bouginage or string cutting operation is often necessary. The contractures are unusually resistant to division.

Syphilis of the small intestine is known to occur. Most cases have been demonstrated postmortem, occasionally at operation. It is most frequent in the newborn. Syphilitic enteritis not symptomatically characteristic, gumma and ulcer frequently multiple ulcers, are recognized. Resulting stenosis has been described. A point of interest is the possibility of diagnosing small intestinal specific stenosis by the x-ray. Though I know of no case reported in x-ray literature there is no question but that the x-ray can determine and localize a small intestinal stenosis. Small intestinal lesions are so rare that the recognition of an otherwise not explained localized stenosis should suggest the possibility of its syphilitic origin. Amyloid degeneration of the small intestine of syphilitic origin is encountered, generally postmortem.

Syphilis of the stomach offers the most fascinating, difficult and withal diagnostically and therapeutically satisfying problem in gastroenterology. Until the past three years considered as so rare as to

be regarded as a curiosity, it has come to be recognized as a clinical entity the possibility of whose presence must be held in mind in the consideration of any gastric neoplasm or atypical ulcer demonstrable by the use of the x-ray. This knowledge has come largely as the result of several studies of adequate numbers of cases from organization of large material. It will only be possible to touch on points of practical interest. Tertiary syphilis affects the stomach in the form of gumma, gummatous ulcer, and most frequently as a secondary mutilating sclerosis. The disease is rare, but occurs much more frequently than previously supposed. It is probably fully as common as syphilis of the rectum. To illustrate its incidence, I may mention that in some five thousand gastrointestinal x-ray examinations I have seen approximately two hundred gastric neoplasms among which were four known cases of gastric syphilis and several others whose luetic origin is highly probable. The x-ray has been the chief factor in the furtherance of our knowledge of the condition. The symptoms are not definite though often severe, constituting a sort of composite picture of peptic ulcer and carcinoma, rather favoring ulcer. The history is usually of suspiciously long duration. The symptomatology is a reflection of the peculiarities of the individual lesion as it is influenced by motor impairment, diminished gastric capacity with resulting esophageal reflux and ulceration. An achylia gastrica or subacidity is usual. Hemorrhage is uncommon. A palpable mass is unusual owing to the high position of the stomach due to its general contraction and the fact that the sclerosis is general rather than localized. The x-ray findings in the main suggest carcinoma. The defect is bilaterally contractural, not sharply localized and has a predilection for the pyloric and lower median portions of the stomach. The patient is anemic rather than malignantly cachectic and is usually suspiciously young.

The best practical diagnostic points are a surprisingly extensive gastric lesion on x-ray examination without the anticipated palpable mass in a patient young for malignancy, not commensurably sick and giving an unduly long and uncharacteristic history and a positive Wassermann. Specific treatment does not always result in betterment if the change in the gastric walls is essentially secondarily sclerotic. Gastrojejunostomy is indicated in some cases failing dietetic measures where there is evidence of definite motor impairment by the x-ray.

The differential diagnosis of cancer of the stomach and gastric syphilis is difficult and most important. It is to be recalled that cancer occurring in syphilitics is more common than syphilis of the stomach simulating cancer. A correct diagnosis can be made in most instances by taking into consideration all factors and is especially aided by skilled x-ray work. The evident inoperability of most of the questionable lesions lightens the responsibility in deciding against operation. In cases of doubt especially if the lesion is not extensive an exploratory is safest. The chances of the patient's dying as the result of exploration are less than that the lesion is cancerous and operable. The question of specific treatment in unexplored cases of apparent gastric cancer on account of the possibility of their being luetic, merits careful consideration.

The theory that syphilis is a predisposing factor in ordinary peptic gastric ulcer is probably incorrect; recent evidence discredits the conception. Syphilitic ulcer occurs but is the expression of disintegrating gumma. Such ulcers are large, sometimes of vast extent, often multiple and irregular. I have a few times encountered prepyloric gastric ulcers of large extent and mass in syphilitics that are so uncharacteristic of ordinary peptic ulcer as to awaken the suspicion of their luetic origin. Two of these were resected. One was a serpiginous ulcer with much deep infiltration several square inches in extent. Both specimens were examined by Dr. Opie who stated that the lesion was not characteristically luetic though rich in lymphoid tissue. It seems probable that these ulcer masses are secondarily sclerotic on an old gummatous basis. Curiously these cases were clinically diagnosed as gastric crises—a proved instance of which I have never seen.

Syphilis of the colon occurs in its distal portion; rectum, sigmoid and anus. Primary lesions occur with great rarity more frequently in the rectum than of the anus. Secondaries in the form of syphilide, mucous patch, and ulcer occur. Syphilitic ulceration is sometimes highly erosive and may result in perforation. The symptoms are those of ulcerative proctitis. As in other parts clinical interest centers in the tertiary lesions which result in a clinical entity of diagnostic and therapeutic importance.

Like syphilis of other parts of the alimentary tract, rectal lues falls clinically into two groups. Those conditions essentially luetic and amenable to specific treatment and those secondarily sclerotic

with a resulting alteration of the picture to one of mechanical motor impairment. Thus of essentially specific interest gumma and gummatous ulcer transitionally passing into scar and sclerosis occur in the distal colon. Contractural sclerosis results in motor impairment through diminution in rectal capacity and the more spectacular most important distal colonic syphilitic lesion, stenosis. The condition has been confused with a supposed gonorrheal stenosis whose existence is much doubted, and by stenosis from nonspecific primarily ulcerative secondarily contractural conditions, from which the stenosis of primarily syphilitic origin has been taught by some not to differ.

It seems to me that as in the instance of syphilis of the stomach the x-ray is destined to throw much light on the question of syphilitic contractures of the lower colon. The situation only awaits some considerable series of individually observed cases such as are now available in gastric lues. It would appear at first sight that the proctosigmoidoscope should be an adequate means of observation. It must be recalled, however, that as a rule by it only the rectum distal to the most definitely strictured point is visualizable. What the sigmoidoscope does not show and what the x-ray does graphically indicate is that the contracture is not localized but is most extensive, involving all the rectum proximal to the stricture and at times flatly the entire rectum and in certain cases probably the lower sigmoid; a fact the therapeutic significance of which as to efforts at dilatation and surgical procedures may be readily inferred. I have observed three such cases, two operatively confirmed. An interesting associated condition striking at operation is the work hypertrophy of the colon proximal to the stenosed area. I know of no reports of such x-ray findings in the literature though the condition was described years ago by the great French syphilographer Fournier, and has been much doubted by more recent writers.

The differential diagnosis is a prime practical point. Two means are available. The proctosigmoidoscope and the x-ray. Sigmoidoscopically the lesion in syphilis is of uniform annular distribution as contrasted to carcinoma, and the sense of rigidity and fixity is greater. In rectal lues while the surface is irregular it is more regularly irregular than in carcinoma. Ulceration in lues is extensive and superficial. In cancer friability is greater. The conditions are highly characteristic to the experienced sigmoidoscopist. The x-ray

findings are strikingly different. In lues the picture is that of a long narrow abnormally direct canal fading gradually into the undilated hypertrophied colon above, instead of the convoluted superimposed shadows of the normal rectum and sigmoid. The findings are in sharp distinction to the localized irregular filling defect of cancer of the lower colon which if obstruction exists is dilated proximal to the stricture an expression of the more sudden development of the stenosis. Failing other differential means recovery and examination of tissue, perhaps best with preliminary operative preparation of the patient, is conclusive.

In addition to alimentary syphilis the disease may affect any extraalimentary organ of the abdomen. It is futile to attempt any sort of résumé of the subject in a few moments. A few points may be recalled. Syphilis of the liver is the most common and probably the best recognized of any visceral syphilitic lesion. It is most frequent in the congenital form, sometimes occurring late even after adolescence. In adults syphilitic liver occurs as an early secondary hepatitis giving a close picture of cirrhosis, as a chronic diffuse hepatitis, as gumma, and as a terminal gummatous sclerosed mutilated botryoid form. Practical clinical points may be suggested in the differential diagnosis of syphilitic liver from the cirrheses and those cases in which a sometimes striking tumor is present, from malignancy. In syphilitic tumor, temperature and a peculiar marked and localized tenderness may be mentioned. Symptoms the result of gummatous pressure, circulatory embarrassment and pseudo-gallstone colic occur. Nowadays the Wassermann is a great help, occasionally the therapeutic test is useful. The melting away of large gummatous liver tumors under antisyphilitic treatment is one of the most spectacular therapeutic results in medicine. The terminal sclerotic forms of specific hepatitis are, of course, not amenable to treatment. Tertiary syphilis of the spleen occurs as gumma and infiltrative fibrosis with hypotrophic pulp, also as work hypertrophy in syphilitic anemia. The splenomegaly is often great. The diagnostic differentiation from splenic anemia, hemolytic icterus, Banti's disease, and so on, is important. A most interesting practical point is that certain cases of syphilitic anemia unresponsive to treatment are due to spirochetal hibernation in the blood vessels of the spleen and may be cured by splenectomy.

Syphilis of the pancreas occurs as gumma and probably intersti-

tial pancreatitis. Conditions are not well understood clinically. Pancreatic achylia it has been taught is a resultant. Means of its clinical recognition are not as yet accurate. An interesting point recently raised is the relation of pancreatic syphilis to diabetes. On studies of incidence conclusions are chiefly against the theory.

Syphilis of the peritoneum though very rare has been described in the form of a pelvic tumor and a miliary tubercle-like lesion of the peritoneum.

Renal syphilis as indicated by gumma is rare. The chief interest as concerns syphilis of the kidney is the occurrence of an acute scarlatinal like nephritis in the primary or secondary stages of the disease. Occasionally syphilitic nephritis becomes chronic.

DISCUSSION

Dr. Wm. Engelbach.—First with regard to abdominal crisis, I feel sure that we have seen some cases of abdominal crisis. I understood Dr. Mills to say that he hadn't seen a case confirmed. My old service at the City Hospital gave me occasion to see some of these cases, tabs could be excluded entirely by spinal punctures and fortunately, 4 or 5 of these cases were repeaters and would come back later on, after they had been examined with apparently negative cord findings, to be positive cases a few years later. Cases have been operated on and explored years before when we had pretty good notes and logical examination made by competent neurologists. I merely speak of that one type of tabs because those cases go to other physicians later when they have all outspoken signs of tabs and the man that gets hold of them last wonders why they were operated on with signs of tabs. We took occasion to put all so-called cirrhosis of the liver on specific treatment, those that had negative Wassermanns and other findings were surprised to see 20 per cent of them clear up entirely. I remember a very interesting case in East St. Louis some time ago in which patient had large massive liver and high leucocyte count, chills and fever, had all classical signs of abscess of the liver. They operated on this case and operation proved to be simple gumma of liver, same cleared up entirely on specific treatment. Dr. Mills, I think, covered the ground so well in gastric syphilis that I feel I can add nothing to it.

I want to report a short summary of cases of ulcer that I saw years ago that first taught me to know that syphilis of the intestinal tract simulates duodenal ulcer. Patient operated on for duodenal ulcer. Gastroenterostomy done and he apparently recovered without any special treatment, returned a couple of years afterwards with same symptoms recurring, same ulcer, same hemorrhages. At that time on reexamination I found that he had other findings, overlooked at first examination, unequal pupils and other findings which looked like specific disease, and we did a Wassermann on him and it was four-plus. We placed him on simple specific treatment, and ulcer symptoms disappeared quickly.

Lesion along the sigmoid so-called diverticulitis has been a confusing thing to us. I know a number of cases that have been operated on and the operator called them malignant lesions, which have cleared up entirely on specific treatment.

Dr. E. Walter Mills (closing).—I stated that I had never seen a case of proven gastric crisis of luetic origin. I threw this bomb advisedly. I have seen quite a number of cases diagnosed as gastric crisis that proved to have ulcer of the stomach. I have no doubt, of course, that gastric crisis occurs, every one seems to know all about it, but it must be a very rare thing, judging by my own experience. If any one will read the classical description of gastric crisis in standard text books on practice of medicine, he will be struck with the similarity of the symptomatology to that of gastric ulcer; especially a certain type of prepyloric ulcer. Certain of these ulcers may not be detected by palpation of the stomach at operation when in the nonsclerotic stage, though giving x-ray evidence. These facts have probably accounted for many cases erroneously regarded as instances of luetic gastric crisis that in reality were due to gastric ulcer in syphilitics.

IX

THE REACTIONS ON THE NERVOUS SYSTEM

BY FRANK R. FRY, M.D.

THAT syphilis is the most frequent cause of organic disease in the nervous system is everywhere conceded. Hence, the importance of interpreting its stamp wherever impressed on the various neurosyndromes. This has proved to be a very practical work and the ardent pursuit of it for many years by clinicians has constituted neurology's important contribution to syphilology. Only those intimately familiar with the history of neurology have a full conception of the volume and the character of this work. By way of illustration, it is well known that even before the discovery of the organism of syphilis, neurologists generally had reached the conviction that paresis and tabes could have but one essential cause. As to how this cause was operative in producing these syndromes there was, as we also know, a great deal of speculation. With the demonstration of the *Spirochete pallida* in the parenchymatous structures of brain and cord these speculations promptly ceased, simply because the clinical structure of these two entities was so complete that it fitted perfectly to the pathology as soon as the latter was convincingly produced. It would be gratifying to recount other instances in which the role of syphilis in other neurosyndromes has been quite as accurately deciphered clinically without the illuminating help of modern pathology and serology. This I must pass, however, and attempt, in the brief time allowed, to give some idea, at least, of the present conception and classification of the reactions of syphilis in the nervous system.

To estimate the value of any single motor, sensory or psychic symptom, it is very necessary to recognize its relation to other symptoms which may or may not be present, hence the importance of determining the groupings of symptoms and of setting forth the same in tangible forms or syndromes.

Beginning with a primary pathologic division of neurosyphilis into (1) meningovascular and (2) parenchymatous, we may make a general clinical classification to comport therewith. However, in our effort for a more comprehensive insight we find we must, in keeping with the data of modern pathology, particularize. We find the terms meningeal neurosyphilis, vascular neurosyphilis and parenchymatous

neurosyphilis; and compounding the same meningoparenchymatous, vasculoparenchymatous and meningovasculoparenchymatous neurosyphilis. In the light of these established tissue findings, a refined clinical enumeration or classification must be correspondingly expansive, or as nearly so as may be.

In collecting the above anatomic data and the clinical pictures reflected therefrom, it is evident that a convenient classification is not a simple matter. For example, in the meninges, the general reaction may range anywhere between a subinflammatory or so-called "anaphylactic" process (with pronounced lymphocytosis but with no clinical signs) to a profuse and intense gummatosis with numerous general and focal clinical manifestations. According to the intensity and regional distribution of these meningeal reactions we find the familiar syndromes of cranial nerve palsies, such as bulbar palsies, ocular palsies, hemiplegia, monoplegias, etc., and in the cord the various types of meningomyelitis, root-neuritis, and the puzzling muscular atrophy syndromes, etc. A side observation may be made at this point to the effect that the reaction of syphilis in the membranes does not often produce the meningitic picture furnished by other infections. Only occasionally is an instance of this kind encountered and even then the diagnosis may usually be made by the presence of signs familiar to the practiced clinician, even independently of the serologic findings.

Continuing the question of classification, if we attempt this from a regional as distinct from a pathologic standpoint, we find that the items rapidly multiply. Take, for instance, the item of hemiplegia: apoplectic, ingravescent, progressive, thalamic types have all been so long recognized that they are familiar syndromes and they may all be caused by syphilis. Going further with the encephalon in a regional classification, there are many other familiar syndromes enacted by syphilis, as, for example, encephalitis, arteritis of various types, cortical and basilar meningitis, tumor syndromes, cerebellar, pontine and bulbar syndromes, etc.

Passing to the spinal cord we are in another region of familiar symptomatology: the various meningetic, myelitic, vascular, degenerative, tumor and other syndromes, the definition of which has been accomplished, often, by masterpieces of anatomic, physiologic and clinical workmanship, are some of the features. Syphilis may, and often does, play a most important role in all of these.

The foregoing citations give us an idea, at least, of the volume of items with which the clinician must be familiar in searching for the signs of neurosyphilis. We may also see therefrom the difficulty of diagraming or arranging the same into useful formulæ for the purpose of classification. The proper valuation of the items in each instance constitutes the practical work of the clinician. That it, in its present proportions, may fittingly become "the work of a life-time" is not overstating its importance.

Speaking of the neuroses and psychoses of syphilis, we hear mention of such items as epilepsy, neurasthenia, insomnia, migraine, headache, mania, melancholia, paranoid states, etc. These, I feel, may all be disposed of by the general observation that syphilis, in common with other diseases, produces constitutional states, often with lowered resistance in individuals predisposed to the above types of neuropathic reactions. However, there are under this head some interesting data that it may be well to notice. For example, the incidence of epilepsy in syphilitics is rather large, but epilepsy and syphilis are both prevalent maladies, hence coincidence must be considered. In a classification of Southard and Solomon, epilepsy is included as occurring in meningeal, vascular, parenchymatous and meningovascular neurosyphilis. But in view of the fact that we do not know either the physiologic mechanism or the immediate pathology of epilepsy, observations of this kind have little practical importance.

The improvement of epilepsy under antiluetic therapy is not a sound basis for concluding that it has in any instance been immediately caused by a syphilitic pathology either inside or outside of the nervous system. For some years past I have seen various epileptics improve under arsphenamine treatment. Recently I have given this drug to several epileptics, who are not syphilitics, on the theory that if any agent has been found really beneficial in one group of epileptics it would be rational to exploit it with others. On the same theory I have given mercurry (mostly by inunctions) to epileptics for many years.

In this connection it is interesting to note an observation to the effect that a considerable percentage of nonsyphilitic epileptics have been found to react in a peculiar or so-called "paradoxical" manner to the Wassermann test in the blood.

Epileptiform phenomena of varying degree and frequency are

often early harbingers of paresis, a fact well known to experienced clinicians, but often overlooked by others.

In the case of neurasthenic symptoms in syphilitics, especially in more acute forms, the examination should extend carefully beyond the nervous system to decide the possibility of syphilis or other causes elsewhere. Visceral symptoms especially should be carefully considered.

The same may be said of migraine and other types of headache. For while syphilitic meningeal headache is in some sense rather characteristic, other possibilities must often be kept in mind.

Concerning the mental manifestations of syphilitics, it may be mentioned that in addition to those characteristic of paralytic dementia, various psychic reactions are often noted. Some of these have been grouped by various authors under the term "pseudoparesis." It is evident, however, that these writers have not all the same conception of either symptoms or pathology in employing this makeshift designation. Some of the cases so characterized certainly turn out later to be true paresis. Others not following this course are probably rare types of encephalitis or of arteritis.

It has been estimated that 25 per cent of paretics present a depressive type of psychic reaction. That many cases present a depressive phase in some stage of their progress is a fact not to lose sight of.

In closing I wish to call attention to a most interesting and equally important item, viz., the fact that the central nervous system is invaded by the treponema early in the course of the general infection. Any doubts or reservations that may have existed about this have been dispelled by the abundant, careful statistics that have appeared, many of them even in recent months. These statistics based on a lymphocyte count in spinal fluids from large and varied groups of individuals during the florid stage of the infection (suitably controlled of course) show conclusively how frequently this invasion takes place in the absence of any reflected clinical signs to betray the fact. The importance of it need not here be enlarged upon. We probably do not yet grasp its full significance.

X

THE REACTION OF THE LUNG

BY LOUIS C. BOISLINIERE, M.D.

THE presence of the *Spirochete pallida* in the lung provokes a response on the part of the pulmonary tissue which finds its expression in the effort of the host to wall off, encapsulate, enmesh and encompass the invader with avascular fibrotic tissue. This reaction is probably, in the beginning at least, of the foreign body type, primarily a fixed tissue cell reaction. If the parasite has been deprived of its virulency, or if its aggressive functions have been diminished by its passage through the natural anatomic barriers before reaching the lung, this reaction may be sufficient to arrest the process, in so far as the lung is concerned. If, however, it has retained its virulency, its specific toxins may vulnerate the adjacent tissue and break down this first line of defense, and, as a result of this further provocation, the surrounding capillaries dilate, leucocytes and other blood elements accumulate, an inflammatory process is initiated, resulting in great cellular infiltration and overgrowth of connective tissue, fibrous and avascular, which again may be sufficient to completely circumvent the further growth and activity of the parasite. So, it is quite conceivable that we may have localized syphilitic anatomic induration in the lung without manifest clinical disease thereof, just as we have anatomic tubercle without clinical tuberculous disease or phthisis. Whereas great overgrowth of fibrous tissue is quite characteristic of syphilitic reaction in the lungs, nevertheless a maximum of deposit may not prove to be the optimum and result in complete englobing of the parasite. The aggressive little enemy insidiously finding avenues of escape, will seek paths to other portions of the lung, and again and again the phenomena of action and reaction recur. It is this continued aggressive action of the spirochete with their weapons of offense on the one hand, and the stimulation of the host to continued reaction with its defenses on the other, that constitutes chronic syphilitic disease of the lung. All the foregoing is very trite, almost axiomatic, but it has been scientifically demonstrated, can be seen to occur, and therefore gives us established and indisputable premises from which definite conclusions may be logically drawn:

1. That syphilitic disease of the lung is a progressive, chronic, in-

flammatory process initiated and continued by the presence of the spirochetes therein, and resulting in certain histogenetic changes quite characteristic of the disease, namely, fibrotic indurations and gummata in which the spirochetes have time and time again been demonstrated. It may attack any and all the structures of the lung, including the pulmonary artery and the pleura. It may be a benign, a latent, or an active progressive inflammatory process, with chronic interstitial pneumonitis, producing profound clinical symptoms.

2. That the physical signs are not distinctive, but are those of a chronic inflammation of the lung, and the symptoms those of a chronic toxemia.

3. That the reaction, meagerly and incompletely referred to above, does not differ essentially, *mutatis mutandis*, from that evoked by the presence of the tubercle bacillus in the lung.

4. That an active syphilis of the lung may attack encapsulated anatomic tubercle, soften the wall, liberate the incarcerated bacilli, and an active pulmonary tuberculosis result as a direct effect of the syphilitic reaction, and thus the two diseases can synchronously exist. When they do, syphilis usually precedes the tuberculosis. Again emphasizing the fact that man, so far as tuberculous disease is concerned, is as safe as the capsule of his tubercle and no safer.

5. That anatomic syphilitic foci may exist in the lungs without manifest luetic disease thereof.

6. That a diagnosis of syphilis of the lungs can not be made with any degree of certainty from physical signs and symptoms alone.

These physical signs and symptoms being closely allied and sometimes identical with the physical signs and symptoms found in the several types of tuberculosis of the lungs, it is quite necessary to see whether a differentiation can be made between the two infections. Clinical observation and autopsy investigation have established the fact that each disease shows marked predilection for certain portions of the lung. Syphilis usually chooses the hilus and central portions of the lung, and tuberculosis the apices wherein to manifest their respective activities. It is rare that we encounter an active tuberculous lesion in the lung that is not connected with the hilum by a continuous peribronchial thickening of the related bronchi. As the syphilitic process may commence in the interlobular septa, along the course of the pulmonary artery or other blood vessels or even in the pleura, isolated patches of induration may occur which are *unconnected* with

the hilus by the peribronchial thickening. This fact is of great value in the interpretation of x-ray pictures and deserves further study. *Isolated* patches of induration, especially if large and not otherwise satisfactorily explained, should suggest strongly their luetic origin. Clinically, syphilis of the lung may be divided into three types: fibroid induration, gummata and sometimes areas of consolidation and exudative inflammation. By far the most common clinical type is fibroid induration accompanied with exudative inflammation; frequently, but not always arising at the hilus, it travels along the peribronchials and assumes a most extensive fibrosis with consequent bronchiectases, the gumma which are almost always accompanied by more or less induration may vary in size from that of a small seed to that of a lemon. Both types may coexist and usually do. Occasionally a gumma undergoes central necrosis, caseates with cavity formation empties into a bronchus causing the so-called syphilitic phthisis. It is a very rare type. Syphilis tends toward fibroid dissemination and bronchiectases; tuberculosis, towards focalization and cavitation. Rales in the lung, being but the expression of action and reaction, can be of every variety and common to both conditions, but if moist they are always the sign of an active process. In syphilis they are usually due to the interstitial pneumonitis and accompanying bronchitis and are of these types. Areas of increased voice conductivity and compensatory emphysemic areas can be demonstrated. In phthisis evidences of definite cavities at the apices of the several lobes are apt to be found.

Bronchostenosis is common in syphilis, rare in tuberculosis; however, none of the physical signs are absolutely and unequivocally distinctive. If the physical signs are at the apices, phthisis is indicated, if at the base or central portion, in the absence of other adequate explanation, syphilis should be borne in mind. Atypical findings in the lung of any kind should arouse our suspicions. In extensive bilateral fibrosis, even if the diagnosis of fibroid phthisis has been established, syphilis should be considered a possible additional etilogic factor. Again in recurrent or chronic asthma and bronchitis, especially if accompanied by fibrosis and bronchiectasis in young children and adolescents, late hereditary syphilis should be thought of as a possible cause. After all is said and done the most constant sign and symptom of syphilis anywhere in the body is a positive Wassermann reaction, and the most constant sign and symptom of tuberculosis is the

presence of the tubercle bacilli in the sputum. The latter is pathognomonic, the other usually so, and justifies corresponding therapeutic attack; as Barker says, "When in doubt have a Wassermann test made. When not in doubt, still have a Wassermann test made." And, I may add, a tuberculosis complement-fixation test at the same time. When there are extensive physical findings accompanied by moisture, and a careful, thorough and complete search, repeated several times, has failed to reveal the presence of tubercle bacilli in the sputum, tuberculosis can usually be ruled out. The clinical symptoms may be identical with those of progressive tuberculosis, but are usually of a milder degree, the most noticeable of which are cough, dyspnea and hemoptysis. Lastly we have the therapeutic test. Under antisymphilitic regime the condition should rapidly improve, and retrogressive striking changes bordering on the spectacular sometimes quickly take place. The diagnosis is largely one of exclusion. Tuberculosis must be excluded or recognized as concomitant: unilateral massive fibrosis, due to pneumokonioses and consequent bronchiectases: simple chronic interstitial pneumonitis, if such a condition ever does exist: abscess of the lung: postgrippal inflammatory deposits: encysted empyema: mycoses: neoplasm: sarcoma and carcinoma: foreign body in the bronchi: brown induration occurring in certain cardiopathies, must all be excluded.

There are no absolutely distinctive criteria in the physical signs and symptoms, we must look for corroborative evidences of unmistakable syphilis in the more accessible organs of the body. Warthin, for instance, has shown pathologically that, next to the aorta and heart, the testes are the most frequent sites of syphilitic infection, in 36 cases 31 showed orchitis fibrosa. Although syphilis of the lung has always been considered an uncommon disease, because of the infrequency with which it has hitherto been found by pathologists, nevertheless there has grown up since the discovery of the spirochete new pathologic criteria, the application of which has revealed characteristic syphilitic lesions with demonstrable spirochetes where they were entirely overlooked by the grosser methods formerly in vogue. Warthin at Ann Arbor found in 750 autopsies evidence of syphilitic infection in 300 cases, or 40 per cent, and Symmers at Bellevue only 314 cases in 4,880 autopsies or 6.5 per cent. Warthin explains this discrepancy, not upon the difference of the clinical material, but upon the different pathologic criteria employed in the two studies. If these

newer and more accurate methods were applied to the lungs, a vastly larger number of syphilitic infected lungs would undoubtedly be revealed.

Does the law of Louis, that after the age of puberty, a tuberculous lesion in any part of the body is almost invariably accompanied by pulmonary tuberculosis, apply in syphilis? Does such a vascular organ as the lung ever *entirely* and *absolutely* escape infection in chronic constitutional syphilis? If, as some think, syphilis in the lung is a late manifestation of the infection and occurs only in untreated or insufficiently treated cases, it could be prevented in all cases by early diagnosis and the prompt institution of proper and sufficient treatment. At best our knowledge of syphilis of the lung is still fragmentary and incomplete.

In conclusion I wish to briefly detail one case, and to present the roentgenograms of it. This case occurred in the service of Doctor John McHale Dean to whose courtesy we are indebted for its presentation.

E. O., male, aged fifty, gave a history of having had active tuberculosis for the previous ten years. Persistent cough, scanty expectoration, frequent fever, occasional night sweats, emaciation, continuous pain in the left chest for the past ten years were the predominant symptoms. Persistent bronchial rales with dullness and flatness on percussion over a large area of left lung. Something in the case aroused Doctor Dean's doubts as to the accuracy of the diagnosis of tuberculous disease. The patient was sent to St. Mary's Infirmary where repeated sputum examinations proved negative to the tuberculosis bacillus. The Wassermann test was four-plus; patient then admitted that he had a chancre fifteen years before. An x-ray (Plate I) was then taken. The left lung shows a dense shadow extending from the base to the third rib. Neither lung structures nor heart can be seen through it. It gives the impression of either a very dense fibrous pleura or a large accumulation of fluid. A number of dry taps were made. Above the shadow in the upper portion of this lung are seen thickened peribronchials and two *isolated* patches, in no way continuous with or connected with the thickened peribronchials, can be easily outlined. The apex proper is a little cloudy, but does not show any "fuzziness." On account of the dense shadow, the hilus on this side can not be seen. The chest was tapped several times in several places, but *no* fluid could be withdrawn. The right lung shows a large and

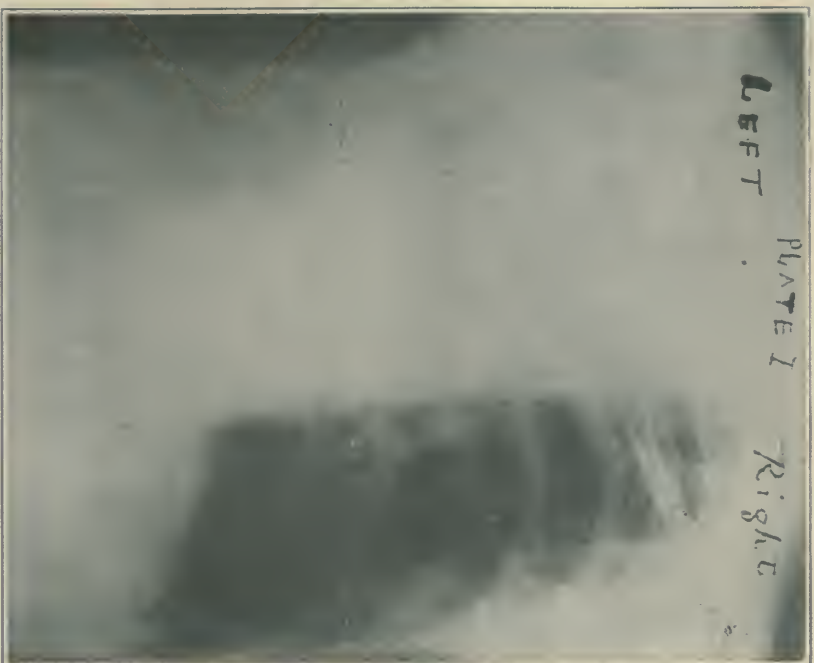


Plate I.—Shows a dense fibrous left pleura, obscuring the heart shadow almost completely. The right lung shows large hilus involvement with thickened peribronchials extending downwards towards diaphragm, also a few isolated patches of indurations unconnected with hilum by thickened peribronchials in upper portion of this lung. One calcified node.

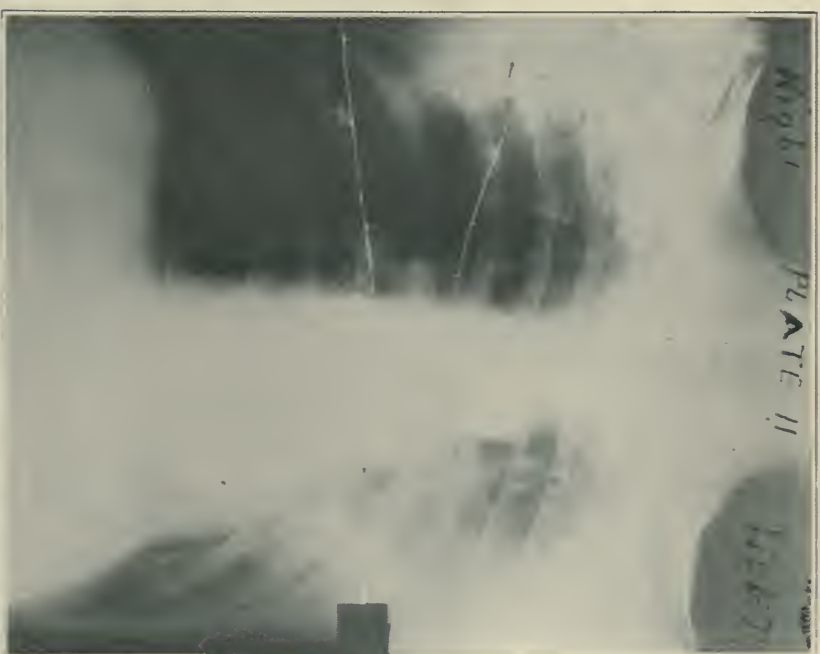


Plate II.—Demonstrates the marked change that has taken place in the left lung after six weeks of intensive antisyphilitic regime. The density of the pleura is greatly diminished, the heart shadow easily seen and lung findings traced. These plates were broken and the cracks show plainly.

dense hilus with thickened peribronchials extending therefrom towards the central portion and base of lung. The apex is perfectly clear. There are several calcified lymph nodes. The patient was given salvarsan and intensive Ki and Hg treatment. Two months later this second picture (Plate II) was made, and the change that has occurred in the left lung in this short time is simply marvelous, almost uncanny. The dense shadow has disappeared, the ribs are plainly visible, the lung structures can now be seen, the heart easily and clearly outlined. The lung presents indurated patches, large dense hilus with thickened peribronchials extending to center and base. Six months later this man reported in apparent health.

Roentgenologic Diagnosis.—Luetic infection of both lungs, much more extensive in the left lung with evidence of definite and extensive pleuritis fibrosa.

Final diagnosis and conclusions are based on: first, extensive and persistent physical findings in the lungs without the presence of bacillus tuberculosis; second, absence of fluid in the chest; third, four-plus positive Wassermann test; fifth, roentgenogram; sixth, marked and rapid retrogression of all signs and symptoms in response to intensive antiluetic medication.

DISCUSSION

Dr. Seelig Simon.—I was very glad that Dr. Boisliniere brought out the fact that tuberculosis and syphilis are undoubtedly interwoven when it comes to diagnosis of either condition, when it concerns the lungs. I was also very glad to hear him mention the fact that syphilis behaves very much the same as does tuberculosis in its early manifestations. I am concerned wholly and solely with the clinical recommendations of syphilis and I am frank to say that I don't believe it can be recommended, and when I say this, I think I am borne out by men who are most interested in lung conditions, that is, in lung tuberculosis. Strange as it may seem, the greater number of syphilitic lung conditions have been reported through dispensaries, or by men working in clinics. The sanitarium physicians who have been looking for syphilitic lung conditions recommend the rarity of the condition. The only valuable and dependable paper I believe that has been published in the last few years regarding syphilis of the lungs, and the man who reports the cases as recommended is one of the greatest tuberculous workers in the country, namely, Landis of Philadelphia, reported six cases of what the author believed to be definite syphilitic diseases of the lungs. He had these patients at an institution for a long period of time as tuberculosis. He was able to demonstrate upper portion of the lungs, all the physical signs we are wont to find in active tuberculosis of the lungs, but strange as it may seem repeated sputum examinations failed to reveal tuberculosis bacilli. After observation from four to

six months Landis came to the conclusion that these individuals might be syphilitic, and on that basis gave antiluetic treatment. Patients recovered and lung signs vanished. That I believe is the only instance at least in the last few years in which syphilis of the lungs was demonstrated. The recommendation of syphilis of the lungs I believe to be about as difficult as anything in lung work. The individual who is unfortunate enough to get tuberculosis is fortunate enough to have that particular form of tuberculosis which is the one we all hope for in the cure of the disease, namely, fibrosis.

Dr. L. C. Boislaniere.—Of course, only the essentials of the subject could be included in the time allotted in this symposium. I have often thought, however, that a man, who once had suffered definite syphilitic attack in the lung, although all physical signs and manifestations may have cleared up under intensive specific treatment, might still harbor spirochetes; and, for that reason, he should be kept under observation for a long time: just as we do with our arrested cases of tuberculosis.

XI

THE REACTIONS IN THE NEWBORN AND GROWING CHILD

BY PHILIP C. JEANS, M.D.*

SYPHILIS in the child, hereditary or acquired, differs in no essential from acquired syphilis of adults. The immaturity and rapid development of the child rather than biologic changes in the spirochete account for the differences in the clinical picture. With the exception of the initial sore which is lacking in hereditary infection, the disease runs the same course of clinical stages in the child and adult. The child is born with the infection already in the stage of general dissemination, clinical signs of which become evident within a few weeks or even at birth as the "early" or secondary stage. A period of recurrences of the early symptoms follows. After a varying period of latency in which the child may present all the outward appearances of good health, one or more of the "late" or tertiary symptoms occur. In the child as in the adult there is infinite variation in the several phases mentioned, especially in the length of the latent period and in the tertiary lesions. It is intended to discuss briefly the chief features by which syphilis differs clinically in the child and adult rather than to attempt to describe the entire symptomatology of hereditary syphilis.

MORTALITY OF EARLY SYPHILIS

Syphilitic infection acts upon the infant, first, by producing specific lesions and, second, by affecting deleteriously the nutrition and development. Most of the deaths due directly to specific lesions result from the ravages of the spirochete before birth. The infant is born dead or, if living, with signs of severe infection. The death rate is extremely high for infants born with obvious lesions of syphilis. Infants showing secondary symptoms at a later time have a less advanced or a less severe infection and as a consequence have a better chance of life. The effect of treatment on the visible lesions leaves nothing to be desired, but nevertheless death frequently occurs as a result of nutritional disturbances. With active secondary syphilis an adult may lose weight and the loss is not considered of importance.

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A similar disturbance in a young infant may lead to its death. The nutrition must be managed with extraordinary care. We have come to look upon proper progress of nutrition as being more important than antisyphilitic treatment if such medication interferes as it not infrequently does when intensively given.

Since the classical picture of infantile syphilis is one of marked and severe symptoms it is necessary to emphasize the fact that an infant may be apparently in perfect health and still be syphilitic. There may be nothing more than a rhinitis and an enlarged spleen, or there may be no abnormality found except a positive Wassermann. Syphilis in infancy has its silent periods as at a later age.

The Wassermann reaction is relatively more useful in childhood than in adult life for the reason that, with certain well-defined exceptions, there is obtained either a clean-cut positive reaction in the presence of syphilis or a definitely negative one in its absence. Of the conditions said to give a positive reaction in the absence of syphilis but few are seen among children in this locality. Of these few, tuberculosis most deserves mention. Not infrequently in the presence of tuberculosis and in the absence of syphilis a weakly positive reaction is obtained. It is obtained with greater frequency when a cholesterinized antigen is used. Such a weak reaction in childhood will usually be found not to mean syphilis. A more careful study of the patient may reveal tuberculosis and a study of the remainder of the family may indicate the absence of syphilis. Syphilis in childhood usually gives complete fixation with the least delicate of antigens.

Just as there is a Wassermann negative interval at the beginning of acquired syphilis, so may there be early in hereditary syphilis. At birth the serum of only about two-thirds of the syphilitic infants will give a positive reaction. A few remain negative for as long as two months or more, even, in some instances, in the presence of active signs of syphilis.

Very recent mercury medication frequently causes a negative reaction in a serum that would otherwise be positive. An interval of at least two weeks should elapse after a mercury injection before a negative reaction is accepted.

There is a class of individuals giving a negative reaction in the presence of untreated syphilis to which many adults and but few children belong. In family studies are found mothers and with even greater frequency fathers who have taken little or no treatment and

who are Wassermann negative though they have had syphilitic children and are, therefore, syphilitic themselves. There is in some individuals a subsidence of the infection, without treatment, to a point at which there are no manifestations and the Wassermann is negative. Though we have observed this subsidence in hereditary syphilis, it usually does not occur until the period of childhood has passed.

After taking into consideration the few factors mentioned above, a positive Wassermann reaction in childhood means syphilis and a negative reaction means freedom from this infection.

CHANGES IN DEVELOPMENT

Of the changes in development resulting from syphilis, those in the teeth are the most important in diagnosis. These changes, when present, constitute good presumptive and almost pathognomonic evidence of former syphilis. They are due to a disturbance of nutrition secondary to a general infection and occur in those teeth whose dentine and enamel are being laid down at the time of such disturbance. The characteristic changes are usually seen only in the permanent teeth, because a constitutional disturbance occurring early enough to affect the deciduous teeth results in death. Which of the permanent teeth are affected and which part of the crown of the tooth depends upon the age of the infant at the time of the constitutional disturbance. This disturbance may be at any time from the sixth month of intra-uterine life to a year or more after birth.

Other developmental anomalies of less diagnostic importance have been described. Hutchinson has recorded defects of the jaw, palate and bony nasal passages. Graves has described defects of the scapula and instances of rudimentary finger nails have been reported. The occasional effect of infection of the nervous system in a very young infant is the arrest of brain development resulting in mental deficiency.

EARLY NEUROSYPHILIS

Infection of the central nervous system occurs with the same frequency in hereditary as in acquired syphilis, the outward evidences of which are in but few respects dissimilar. General convulsions are not uncommon in infancy as a result of meningeal syphilis. They are not usually accompanied by fever; they may recur at very short intervals or they may be separated by several weeks or months. In

late and unfavorable cases convulsions may continue to recur as epilepsy even though the patient is treated to a serologic cure.

THE SKIN AND MUCOUS MEMBRANE

Lesions of the disseminative or secondary period are with a few exceptions very similar to those found in adults at the same stage. Adults do not have the extensive infiltrative processes of the skin that are occasionally seen in severe infections in young infants. The most common site for this lesion is about the mouth. Untreated, this inflammatory process remains quite chronic, causing deep bleeding fissures which always radiate from the mouth. On healing these fissures leave depressed radiating scars (rhagades) which are permanent, and which, because such fissures occur in no other condition, are pathognomonic of severe early syphilis. A similar lesion may rarely occur about the anus and deep infiltration without the radiating fissures may sometimes occur in the skin in other parts of the body. A mild infiltration of this character is very common in the palms of the hands and the soles of the feet. The skin of the palms and soles is red and shiny and the process is attended by desquamation. Slight desquamation of the palms and soles is not uncommon in young infants from other causes, but the peculiar appearance of the skin of these parts seen in syphilis can scarcely be mistaken for anything else.

The muddy, coffee and milk appearance of the skin so often seen in infantile syphilis is due in some measure to anemia which is caused in part by the systemic effects of the infection and in some instances also by some involvement of the marrow cavity of the long bones. This waxy pallor is caused in an even greater measure by cutaneous inflammation with thickening and cellular infiltration.

Though adults may have a mild rhinitis during the secondary period, there is never seen the severe involvement so common in hereditary syphilis. Rhinitis in infancy may be so mild that its significance is overlooked, or there may be a profuse blood-stained discharge with complete occlusion of the nose. Rhinitis of greater or less severity occurs in the majority of syphilitic infants and is, therefore, a valuable diagnostic symptom. The reason for the greater severity of the skin and mucous membrane lesions in infancy may be the greater vascularity of these structures at this age.

EPIPHYSITIS

Points of increased vascular supply seem especially likely to be the seat of syphilitic lesions. Such a susceptible point in infancy is the rapidly growing portion of the long bones. A lesion at this point is spoken of as epiphysitis, though more correctly it is an osteochondritis. It occurs at the line of ossification and is the most constant and characteristic lesion of early hereditary syphilis. Ossification is delayed and the area becomes thickened. In extreme cases the lesion may have a stunting effect upon the growth. This lesion is best observed at necropsy and fairly well by roentgen rays. A relatively small proportion of infants have obvious clinical evidence of this disturbance. In these few there is swelling, pain and loss of function resulting in a pseudoparalysis.

SPLENIC ENLARGEMENT

There is some dispute as to the frequency of splenic enlargement in the secondary period of syphilis of adults, some maintaining that it rarely occurs. There can be no such question in infantile syphilis, for the spleen is palpably enlarged in the majority of instances. The finding of such enlargement, however, is of but minor help in the diagnosis, because hyperplasia of the spleen is found in infants in numerous conditions having no relation to syphilis. There is also a general adenopathy in both hereditary and acquired syphilis. In this respect the most helpful finding in infancy is enlargement of the epitrochlear glands, marked bilateral enlargement of which in the absence of pyogenic infection or history of such infection constitutes presumptive evidence of syphilis.

RECURRENCES

The period of recurrences is remarkably similar in hereditary and acquired syphilis. In infancy the manifestations recur chiefly as mucous patches and condylomata, the latter being much more frequent. Recurrences are usually confined to the first two or three years of life but may occur as late as five or six years. The finding of mucous patches or condylomata after eight or ten years of age is presumptive evidence that the infection has been acquired.

LATE SYPHILIS

Practically all of the lesions that we know as belonging to late acquired syphilis can and do occur as a late result of hereditary syph-

ilis. However, some of these lesions are exceedingly rare in the period of childhood. Cardiovascular changes so common in adults with syphilis are almost unknown in childhood. Certain visceral changes, such as cirrhosis of the liver are quite rare. Classical tabes and paresis occur as the result of hereditary syphilis, but they do so rather rarely in the period of childhood. To what extent these lesions occur in adults as a result of hereditary syphilis is not certain, but what is certain is that they do occur. On the other hand, interstitial or parenchymatous keratitis, which is very common in childhood, is very uncommon in adults, and when it does occur is practically always a result of hereditary infection.

In the order of their frequency the structures commonly involved clinically in late syphilis in childhood are the eyes, nervous system, bones, joints and the mucous membranes of the nose and throat. The triad of manifestations described by Hutchinson as being useful in the diagnosis of hereditary syphilis is of but little aid in this locality because of the infrequency with which it occurs. A somewhat more frequent, and therefore a more useful triad, has been suggested, viz., Hutchinson's teeth, keratitis and synovitis of the knees.

It is important to look upon syphilis as a familial disease. Frequently all of the brothers and sisters, as well as the parents of a syphilitic child, are found to be infected. The examination of other members of the family is often a great help in the diagnosis of doubtful cases.

In conclusion and summary it is emphasized that the spirochete of syphilis behaves in the same manner whether it is acquired by inheritance or later in life. The clinical manifestations differ in the early stages because in infancy the rapidly developing structures are more profoundly affected than are the same structures fully developed. They also differ for the reason that certain parts, merely because of rapid growth, are highly vascular, and such vascular areas are more likely to be affected or are affected more severely. Later in childhood when the development is slower or more nearly completed the manifestations of syphilis approach much more closely the types found in adults with acquired syphilis.

DISCUSSION

Dr. W. W. Graves.—I should like to discuss briefly Dr. Jeans' reference to the scaphoid type of scapula as a possible sign of syphilis.

This type of scapula was found by me in 1906, and described and named in

1910. In the course of my studies I have found that syphilis is one disease factor affecting presumably the germ plasim of parents, and thus producing various anomalies in the progeny, among which is the scaphoid type of scapula, but there may be various disease factors and whatever these may be they are, doubtless, insignificant when compared with the factor of heredity in the causation of heritable variations in man. I have never considered the scaphoid type of scapula as a sign of syphilis in the individual, though I have repeatedly pointed out a *connection* between syphilis in the parents or more remote ascendants and the scaphoid type of scapula in the progeny. My studies have shown that the scaphoid type of scapula is present in varying degrees and percentages in all races in our population and among all ancient races thus far examined, including the *pre-dynastic* Egyptians. In modern man it is found with great frequency among the young but it is relatively infrequent in the old, and it is most frequently found in any period of life among those who deviate markedly from an ideal in physical development. If we may assume that among humans as among all living things there are the weak as well as the strong, then the scaphoid type of scapula may be considered as an index, rough though it be, of the inherent qualities of the protoplasm peculiar to the individual.

Many physicians have misinterpreted my writings on the scaphoid type of scapula in considering it a sign of syphilis when as a matter of fact it should never be so considered. If it has any meaning at all as a sign, it is that of deviation, but it can not be so interpreted in every case, because some of the best human types have this form of shoulder blade.

The scaphoid type of scapula in itself should never be considered a sign of syphilis but rather as a sign of deviation. The causation of deviation may be various disease factors, including syphilis, affecting either the germ plasim or the environment in utero, but its chief causation is heredity. The only means we have for determining the causation of deviations is by making comparative studies of whole families using the parents and more remote ascendants and collaterals as standards for comparison. Such studies will show that the scaphoid type of scapula can in no case be considered as a sign of syphilis in the individual possessing it. Nevertheless, through family studies, it may often be interpreted as a sign of *deviation* for which some disease factor, or heredity, or both, may have been responsible.

XII

THE REACTIONS IN WOMEN

BY GEORGE GELLHORN, M.D.

NO ONE can speak of syphilis in women without first mentioning some of the differences of the disease in the two sexes. The classical signs with which we have become familiar from thousandfold observations on the male, will be found wanting or considerably modified in the majority of our women patients. While in men, the initial lesion is usually noticed by the patient and found by the physician without any difficulty; and while in men the primary sore leaves unmistakable traces behind which may persist for a long time, the opposite is true in women. The difficulty of demonstrating a hard chancre in women is due to two factors. The female genitalia being more complex than the male, the sore might be established in some concealed location and thus escape discovery. Chancre in women is smaller than in men. Only if situated on cutaneous surfaces about the genitals, does it present the typical induration. Upon the genital mucous membranes the parchment-like induration of the base is usually absent and can only very occasionally be elicited. Furthermore, the primary lesion clears up more rapidly in women than men. The ephemeral nature of the primary lesion in women is so pronounced that, to speak with Shillitoe, in a marked case of secondary syphilis, a medical man need have no doubt as to the correctness of his diagnosis because he has failed to discover the original sore.

The transient nature of syphilitic affections of the genital mucosæ in women seems to prevail throughout the course of the disease, and even deep ulcerative syphilides of the cervix uteri leave, as a rule, no scars as typical as those of syphilitic ulcerations in other mucous membranes. Mucous patches in the oral cavity occur probably as frequently in women as in men, but the comparative absence of chemical irritation due to smoking and drinking, favors a more rapid limitation and complete resolution of these luetic manifestations in the majority of female patients. Cutaneous eruptions are likewise milder and more fleeting in women. The only notable exception is found in the so-called collar of Venus, or leucoderma cervicis. These white spots which are irregularly distributed over the neck, represent remnants of an annular syphiloderm and persist in women for so

long a time and in such a pronounced form that they may safely be regarded as pathognostic.

The general health may be little affected during the eruptive stages of the disease; a man may present a well-marked eruption and yet feel perfectly well. For some reason which can not yet be explained, the female sex in some respects seems to suffer more than the male. Fever and anemia are commoner in women than in men, and an obscure cachexia in a younger woman should make us suspect syphilis as the underlying cause. Very often, however, there are no outward signs to guide us in our clinical diagnosis, neither are there any suggestive points in the history of the case, and it was left to the systematic employment of laboratory aids to establish the fact that the so-called latent syphilis is considerably more frequent in women than in men.

This comparison of the reactions of syphilis in the two sexes would be incomplete without a reference to the relative infrequency of tabes and paresis in women. This phenomenon may be explained in two ways. It is possible, as has long been claimed, that syphilis is actually less frequent in the female. On the other hand, it may well be that in men the symptoms of neurosyphilis are very promptly recognized as such, whereas in women the correct diagnosis is only too often hampered by a superficial assumption of genital or climacteric ailments.

Proceeding to the reactions of syphilis in the gynecologic field proper, it will suffice to state that early and late manifestations of lues occur in all the female reproductive organs. While the specific lesions upon the external genitals are well known, the idea prevails that those of the internal genitals are extremely rare, but after an exhaustive study extending over a period of more than seven years, I have come to the conclusion that, in the past, we have not found these lesions because we did not look for them, or because we interpreted them incorrectly. I believe that many an erosion which resisted every form of local treatment was in truth a syphilitic ulceration. Indeed, it was just such a case that started me on a systematic investigation after I had succeeded in recognizing the condition and avoiding the operation for which the patient had been referred to me. I am convinced that a good many uterine cancers that were permanently cured after simple hysterectomies, were in reality gummata of the neck of the uterus. There is quite an extensive literature on presumably

inoperable cancers of the uterus which disappeared readily after antisymphilitic treatment had been instituted. Two such cases have come under my own observations. One was cured promptly and, so far as I know, permanently. The other occurred in a tabetic woman who remained refractory to all treatment.

As time progresses and as we learn to pay more attention to the possibility of luetic lesions in the genital sphere of women, we shall avoid these diagnostic mistakes. We shall also recognize more fully than heretofore, the correct interpretation of functional disorders such as menorrhagias and particularly amenorrheas which are so often produced by syphilis and which offer so grateful a field to causal therapy.

Syphilis may not merely resemble cancer but it may also produce cancer. In the field of oral surgery it has long been known that cancers of the tongue and lips frequently start on the basis of former syphilitic lesions, and the same is true of a certain number of genital cancers in women. At least, I myself have seen two cancers, one upon the vulva, the other upon the cervix, develop from syphilitic ulcerations in these respective localities.

The role of syphilis in obstetrics has been well studied. Miscarriages and stillbirths follow in the wake of the disease, and the sad fate that awaits the hereditary syphilitic child has been considered in another part of this symposium. Not only is the quantity and quality of the offspring affected by syphilis, but the mothers themselves are exposed to lasting detriment. A number of cases of abnormal rigidity of the cervix in labor have been reported as having been caused by previous syphilitic lesions. Not long ago, we had at the City Hospital a pregnant woman with a syphilitic elephantiasis of the vulva which remained unaffected by specific treatment. As the tumor mass presented an absolute obstacle to natural delivery Cesarean section had to be performed, but the weakened organism of the patient succumbed to the operation. Thus the seriousness of the disease to both mother and child imposes upon the obstetrician the great responsibility to establish a timely diagnosis and to pursue an energetic treatment of syphilis in the prenatal care of the prospective mother.

Other problems which are intimately connected with the subject of syphilis in women, are the question of syphilis and marriage, and the evil of prostitution. The physician of today can no longer confine himself to the treatment of a group of patients or a category of ailments—he must take active part in the field of social medicine if

he wants to do full justice to the privilege of being the guardian of public health.

It is understood that in this hurried review only head lines, as it were, could be presented and that details had to be suppressed for the sake of brevity. In closing this symposium in which I have taken only a small part, let me acknowledge that I have profited greatly by the papers which preceded mine. This symposium has focused the searchlight of attention upon the syphilitic patient and has served to emphasize these main facts—that insidiously and in a thousand disguises, syphilis may occur in all classes and categories of human pathology; that the aid of the laboratory is of the greatest and inestimable value in combating the disease; but that our diagnosis and treatment should be based first and foremost upon *clinical* study and observation of the syphilitic individual.

STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. X*

A STUDY OF METHODS FOR THE PREPARATION AND PRESERVATION OF HEMOLYSINS

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A LARGE number of methods have been proposed for the immunization of animals for the production of hemolysins; indeed it would appear that the majority of experienced serologists have adopted a method more or less individual in which they have learned to place much confidence. Different animals have been employed and particularly the rabbit, goat, guinea pig, and horse; Noguchi and Bronfenbrenner¹ have found that the rabbit is best adapted for the production of antihuman hemolysins. The doses of corpuscles injected vary considerably in the different methods which have been proposed, as likewise the route of injection and the intervals between injections.

Since the choice of a hemolytic system for the complement-fixation test is influenced by the ease or difficulty with which hemolysins may be produced, one of the special objects of our investigation was to study hemolysin production in rabbits to injections of sheep, human, hen, guinea pig, rat and beef corpuscles with special reference to sheep and human cells.

Just what portion of erythrocytes is concerned in the production of hemolysins has been the subject of investigation by others but with varying results; Bordet,² for example, believes that the stroma of cells produces hemolysin, while Nolf³ believes that this portion produces hemagglutinins and extracts of the cells the hemolysin. Bradley and Sansum⁴ regard hemoglobin as antigenic, but Ford and Halsey⁵ were unable to produce hemolysins with purified hemo-

*Investigation aided by funds accruing from the preparation of arsphenamine.
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globin; Levene⁶ likewise found that injections of pure crystalline hemoglobin failed to produce hemolysins, while solutions of erythrocytes in one-half per cent solutions of sodium bicarbonate were antigenic. It would appear, therefore, that some constituent of the erythrocyte other than hemoglobin is concerned in the production of hemolysins; the stroma are surely antigenic, and Bennett and Schmidt⁷ have recently found that a CO₂ globulin from washed erythrocytes or a substance intimately associated with it, is the antigen concerned in the production of hemolysins.

A troublesome feature in the production of antihuman hemolysins in rabbits is the coincident production of hemagglutinins; attempts to concentrate the serum hemolysins as by Kosakai⁸ and Gilbert and Van Saun⁹ have not succeeded in ridding the sera of these agglutinins. The investigations of Sands and West¹⁰ in these laboratories, have yielded promising results in this direction, indicating that desiccation and methods of filtration tend to remove the agglutinins. Whether or not the erythrocytes can be fractionated for the portion concerned in the production of hemolysins only is problematic, but worthy of investigation because of the practical value such a method would possess in the preparation of antihuman hemolysin.

That rabbits vary greatly in reaction to injections of the erythrocytes of different animals is well known; for example, the majority of animals readily produce hemolysins for sheep and ox cells and poorly for human, chicken, and guinea pig cells; with the latter the death rate among the immunized animals is high and the majority succumb before their sera are sufficiently hemolytic, while with the former the death rate is almost negligible. These deaths are usually ascribed to anaphylaxis, but very probably not all fatalities are to be ascribed to this phenomenon, inasmuch as they occur despite the greatest care in washing the cells free of serum and when the injections are so closely spaced as to render an anaphylactic reaction highly improbable. It is significant in this connection that injections of washed human erythrocytes into rabbits is followed by a marked production of hemagglutinins, and we believe that *these hemagglutinins are largely responsible for the deaths of rabbits receiving injections of human red blood cells rather than anaphylaxis*; the sera of rabbits receiving injections of sheep or ox cells are almost free of hemagglutinins, for these cells and these

animals rarely succumb despite the fact that the same technic is employed and the chances for anaphylaxis equally as good. So far, all attempts to render the human erythrocytes used for injection non-susceptible to agglutination *in vivo* have failed except a method of exposing them to the serum agglutinins *in vitro* and saturating the cells with the agglutinins prior to injection as described later in the sensitization of antigen; this method, however, is not practical as a routine measure by reason of the large amount of serum required and the danger attending the intravenous injection of agglutinated corpuscles.

PURPOSES OF INVESTIGATION

Our main interests were centered upon the production of rabbit antihuman hemolysin inasmuch as human cells are so likely to kill rabbits by reason of agglutination *in vivo*, anaphylaxis, direct toxicity, or a combination of these factors rendering the production of potent hemolysins a relatively difficult procedure as compared with the production of antish sheep and antioox hemolysins. We have gathered from the literature a description of several methods advocated by those who employ an antihuman hemolytic system and especially designed to avoid fatal anaphylaxis and have submitted these methods to comparative trials under the conditions described in the technic.

Since sensitized bacterial vaccines are regarded by many immunologists as possessing superior antigenic values as compared with plain vaccines we have included in our studies an investigation of the immunizing power of sensitized erythrocytes as compared with plain cells not only for the purpose of studying the relative merits of plain and sensitized erythrocytes in the production of hemolysins, but also for the possibility of shedding additional light on the subject of the comparative merits of plain and sensitized antigens in general; furthermore these sensitized cells were for the most part insusceptible to agglutinins and their administration proved interesting not only from the standpoint of hemolysin production, but in relation to the death rate as well.

In our work rabbits were immunized with washed human, sheep, hen, guinea pig, rat, and beef erythrocytes; the purposes of the study may be summarized as follows:

1. To determine the relation of route of injection, dose of cells,

and intervals of injection to the production of antihuman and anti-sheep hemolysins.

2. A special comparative study of the various methods advocated for the production of antihuman hemolysins.

3. A comparative study of the production of hemolysins for sheep, human, hen, guinea pig, rat, and beef corpuscles in rabbits.

4. A study of the relative antigenic properties of plain and sensitized antigens.

5. A study of methods for the collection and preservation of hemolysins.

The serum of each animal was titrated at frequent intervals for hemolysin and in the antihuman series for agglutinin as well; the latter titrations were included as a possible further index of the immunizing value of the respective methods employed and to determine the relation between hemolysin and agglutinin production with the various methods.

TECHNIC

In published descriptions of methods advocated for the production of hemolysins the dose of cells is not given per body weight of the rabbit; since our work aimed to compare the methods it was necessary to reduce the technic to a quantitative basis following as nearly as possible the technic described by various authors. For this purpose we assumed that the doses of cells stated in published accounts were for animals weighing about two thousand grams. Even under these conditions the individual variation among rabbits has required the use of a large number of animals for each method in order to arrive at but general and broad conclusions.

Our animals weighed from one thousand five hundred to two thousand five hundred grams, and represented different kinds, as the pure white, white and black and grey rabbit; both sexes were used, but pregnant females were excluded.

Each animal was weighed before each injection of cell suspension and the dose administered per kilogram of weight.

Preliminary bleedings were made from the ears of each animal and the heated sera tested for natural hemolysin and agglutinin for the particular erythrocytes to be employed in the immunization. Subsequent bleedings were made at intervals after each injection and usually just before an injection of cells was made and the

amount of hemolysin determined in a series of titrations employing dilutions of heated serum, 0.1 c.c. of a 1:10 dilution of mixed guinea pig complements and 0.1 c.c. of a 5 per cent suspension of the corresponding washed cells with a total volume of 2 c.c. and water-bath incubation of one hour at 38° C. *The results expressed in the tables show the highest dilutions of each immune serum in dose of one cubic centimeter producing complete hemolysis under these conditions.*

The agglutination tests were conducted in the same manner, omitting complement. *The values expressed in the tables show the highest dilution of each serum in dose of one cubic centimeter producing macroscopic agglutination of 0.1 c.c. of a 5 per cent suspension of cells after one hour incubation in a water-bath at 38° C. The results were read as positive when clumps of cells were produced which could not be broken up by vigorous agitation.*

In some experiments active immune sera were titrated for hemolysins and agglutinins in order to measure the total hemolytic activity of each serum including the thermolabile hemolysins and agglutinins but *the results given in the tables show the content only of the thermostable hemolysins and agglutinins* inasmuch as the sera were regularly heated at 56° C. for half an hour prior to titration unless otherwise stated.

For purposes of immunization and titrations sheep blood was secured in an abattoir and defibrinated; human blood cells were secured from clots of blood submitted for the Wassermann test. In all instances the bloods were filtered through cotton and washed repeatedly with large volumes of salt solution in order to thoroughly remove all traces of serum.

No special precautions against contamination were taken in the collection and washing either of the human or sheep bloods. In no instance have abscesses developed in the internal organs following the intravenous injection of these cells, although a few infections followed the subcutaneous and intraperitoneal injections. From these results we conclude that with ordinary care in the collection and washing of erythrocytes the blood of the rabbit is sufficiently bactericidal to destroy the bacteria of contamination to be found in cultures of the suspensions of erythrocytes, although large doses injected intraperitoneally and subcutaneously may not be sterilized by the defenses of the rabbit.

For purposes of intraperitoneal immunization therefore, blood should be collected and washed with aseptic precautions or some attempt made to sterilize the cells before injection. We have conducted a series of experiments along these lines with washed and unwashed human and sheep bloods contaminated with staphylococci, with solutions of formalin, bichloride of mercury and mercurophen. The mercurial proved too hemolytic for purposes of sterilization and particularly with washed cells,¹¹ but satisfactory results were obtained with formalin after the following method:

1. Human and sheep blood collected as described above were centrifuged and the cells washed three or more times to remove all traces of serum.

2. After the last washing the packed cells in centrifuge tubes were suspended in five volumes of a 1:200 dilution of formalin in physiological saline solution, stoppered with sterile rubber stoppers and placed in the incubator for one hour followed by thorough centrifuging.

3. The supernatant formalized salt solution was carefully removed, the corpuscles suspended in sterile saline solution and employed for injection.

Traces of formalin may adhere to the cells but not in sufficient amounts to prove toxic for rabbits as injected in the suspensions stated in this paper and hemolysin production does not appear to be affected.

For purposes of sensitization each cubic centimeter of washed cells was immersed in an amount of hemolytic serum representing four times the smallest amount necessary to hemolyze these cells if sufficient complement were supplied; sensitization was permitted to take place overnight at a temperature of about 9° C. followed by repeated washings in large volumes of salt solution to remove all traces of serum.

Part 1

METHODS PROPOSED AND EMPLOYED IN THIS INVESTIGATION FOR THE PRODUCTION OF ANTIHUMAN HEMOLYSIN

The following methods have been proposed for the production of antihuman hemolysin; after a description of each method as described by its author, we have given the technic employed by us in using the method.

1. *Noguchi's Intravenous Method*.¹²—Inject 4 c.c., 3 c.c., 4 c.c., 3 c.c., and possibly another 4 c.c., with four- or five-day intervals; bleed nine or ten days after the last injection.

We injected 2 c.c. of washed human cells per one thousand grams of weight every five days; each dose was diluted with about 8 c.c. of sterile salt solution.

2. *Noguchi's Intraperitoneal Method*.¹²—Inject at four- or five-day intervals; bleeding nine or ten days after last injection. Doses 5, 8, 12, 15 and 20 c.c. of washed human corpuscles.

We injected the following doses per kilogram of weight at intervals of five days: 2, 4, 6, 7 and 10 c.c. diluted with about an equal volume of sterile salt solution to facilitate injection.

3. *Thompson's Method*.¹³—Inject intravenously 0.1 c.c. washed cells every day for three or four weeks. This method was adopted after the work of Coca²⁰ showing that powerful hemolytic sera for sheep cells may be produced by this procedure.

We injected intravenously 0.1 c.c. of washed cells per kilogram of body weight every day for three or four weeks; each dose was diluted with salt solution to facilitate injection.

4. *Craig's Method*.¹⁴—Inject intravenously 1 c.c. of washed erythrocytes every other day until five or six injections have been given; two or three more injections may be required.

We injected 0.5 c.c. washed cells per kilogram of weight every other day; each dose was diluted with sufficient salt solution.

5. *Vedder's Method*.¹⁵—Inject intravenously 0.5 c.c., 1 c.c., 2 c.c., and 3 c.c. washed and packed human cells at five to seven days interval; the last injection of 3 c.c. may have to be repeated several times.

We injected 0.2 c.c., 0.5 c.c., 1 c.c., and 1.5 c.c. washed and packed human cells per kilogram of weight every seven days; each dose was diluted with sufficient salt solution to facilitate injection.

6. *Bronfenbrenner's and Schlesinger's Method*.¹⁶—Rabbits are injected intravenously with washed red cells at four-day intervals; in order to avoid anaphylactic reactions, each intravenous injection, beginning with the third one, is preceded by a desensitizing intraperitoneal injection of the same cells given one-half hour in advance.

The authors have not stated the doses they inject; we carried out this method by giving two intravenous injections at intervals of

five days of 2 c.c. of washed cells per kilogram of body weight diluted with sufficient salt solution. Starting with the third injection we gave 0.5 c.c. per kilogram of weight intraperitoneally one-half hour before the intravenous injection of 2 c.c. per kilogram of weight. Subsequent doses were given in the same manner and of the same doses per kilogram of weight. In addition to these methods rabbits have also been immunized after the following plan:

7. *Subcutaneous Method*.—Rabbits were injected subcutaneously every five days with 0.2 c.c. washed cells per kilogram of weight and diluted with sufficient salt solution to facilitate injection.

8. *Intraperitoneal injection* of 5 c.c. of plain washed cells per kilogram of weight every seven days.

9. *Intraperitoneal injection* of 3 c.c. of plain washed cells per kilogram of weight every three days.

10. *Intravenous Injection of a Solution of Erythrocytes in Water*.—A 10 per cent solution of washed human cells in sterile distilled water was thoroughly centrifuged and filtered and injected intravenously in doses of 10 c.c. per kilogram of weight every seven days.

Inasmuch as our antihuman hemolytic sera were used unheated and contained hemagglutinins we were unable to apply these methods with sensitized cells employing the intravenous route of injection; accordingly the immunizing activity of sensitized human cells compared with plain human cells was studied only in those series of rabbits receiving intraperitoneal and subcutaneous injections; with sheep cells hemagglutination was not encountered and sensitized cells were injected intravenously as well as intraperitoneally and subcutaneously.

Part 2

RESULTS OF IMMUNIZATION WITH HUMAN CELLS

1. *The Production of Hemolysins and Agglutinins*.—Even though the suspensions of cells were prepared with care and injected strictly according to the body weight of each animal, the individual variations in antibody production were quite marked and permit only of broad and general conclusions.

The results are best presented in a series of abbreviated tables to give them as a whole; the results in hemolysin production are shown in Tables I to X and of agglutinin production in Tables XI to XX.

TABLE I

THE PRODUCTION OF ANTIHUMAN HEMOLYSIN BY THE INTRAVENOUS INJECTION OF
2 C.C. PLAIN WASHED CELLS PER KILOGRAM OF WEIGHT EVERY
5 DAYS (NOGUCHI)

TITERS AFTER INJECTIONS							
PRELIM.	1 IN- JECTION	2 IN- JECTIONS	3 IN- JECTIONS	4 IN- JECTIONS	5 IN- JECTIONS	6 IN- JECTIONS	7 IN- JECTIONS
—*	—	1:10	1:10	1:20	1:40	Died	0
—	—	1:20	1:30	1:30	1:60	1:70	1:80
—	—	1:10	1:20	1:30	1:40	1:80	Died
—	—	1:15	1:20	1:40	Died	0	0
—	—	1:20	1:20	1:30	1:40	1:40	1:60
—	—	1:10	1:15	1:20	Died	0	0

*— = no hemolysis in 1:10.

TABLE II

THE PRODUCTION OF ANTIHUMAN HEMOLYSIN BY THE INTRAPERITONEAL INJECTION
OF INCREASING DOSES OF PLAIN CELLS (AFTER THE METHOD OF
NOGUCHI) AND OF SENSITIZED CELLS EVERY 5 DAYS

CORPUSCLES	PRELIM.	1 INJECT.	3 INJECT.	4 INJECT.	5 INJECT.	6 INJECT.	7 INJECT.	8 INJECT.
Plain	—*	—	1:16	1:60	1:100	1:100	Died	
"	—	—	1:10	Died				
"	—	—	—	Died				
"	—	—	1:12	1:20	1:20	Died		
"	—	—	1:10	1:20	1:20	Died		
"	—	—	1:10	1:16	1:30	1:30	1:60	1:80
"	—	—	—	1:12	1:20	1:50	Died	
"	—	—	1:10	1:30	1:30	1:60	1:80	1:80
Sensitized	—	—	—	Died				
"	—	—	—	1:10	1:20	1:25	Died	
"	—	—	—	1:10	1:16	1:30	1:50	Died
"	—	—	—	1:10	1:20	1:40	1:40	1:60
"	—	—	—	1:16	1:30	1:50	1:50	1:80
"	—	—	1:10	1:10	1:18	1:20	1:30	Died

*— = less than 1:10.

TABLE III

THE PRODUCTION OF ANTIHUMAN HEMOLYSIN BY THE DAILY INTRAVENOUS IN-
JECTION OF 0.1 C.C. WASHED PLAIN CELLS PER KILOGRAM OF WEIGHT
(COCA-THOMPSON METHOD)

PRELIMI- NARY	4 INJECT.	8 INJECT.	11 INJECT.	15 INJECT.	18 INJECT.	21 INJECT.	32 INJECT.
—*	—	—	1:10	1:10	1:40	1:50	
—	—	—	1:10	1:100	1:80	1:100	1:100
—	—	—	1:12	1:20	Died		
—	—	—	1:18	Died			
—	—	—	—	1:20	1:30	1:40	1:100
—	—	—	—	1:10	1:20	1:30	

* = no hemolysis.

TABLE IV

THE PRODUCTION OF ANTIHUMAN HEMOLYSIN BY THE INTRAVENOUS INJECTION OF 0.5 C.C. WASHED PLAIN CELLS PER KILOGRAM OF WEIGHT EVERY OTHER DAY (AFTER THE METHOD OF CRAIG)

PRELIMI- NARY	3 INJECTIONS	4 INJECTIONS	6 INJECTIONS	7 INJECTIONS	9 INJECTIONS	10 INJECTIONS
—*	—	—	—	1:10	1:25	1:40
—	—	—	1:25	1:40	1:50	1:80
—	—	1:25	Died			
—	—	1:15	1:60	Died		
—	—	1:10	1:70	1:70	1:80	Died
—	—	—	Died			

*— = less than 1:10.

TABLE V

THE PRODUCTION OF ANTIHUMAN HEMOLYSIN BY THE INTRAVENOUS INJECTION OF 0.2 TO 1.5 C.C. PLAIN WASHED CELLS EVERY 7 DAYS (VEDDER)

PRELIMI- NARY	1 INJECTIONS	2 INJECTIONS	3 INJECTIONS	4 INJECTIONS	5 INJECTIONS	7 INJECTIONS
—*	—	1:10	1:20	1:30	1:40	1:80
—	—	—	1:10	Died	0	0
—	—	1:15	1:20	1:30	1:50	1:90
—	—	1:15	1:30	1:30	1:40	1:80
—	—	Died	0	0	0	0
—	—	1:10	1:30	1:30	1:60	Died

*— = no hemolysis 1:10.

TABLE VI

THE PRODUCTION OF ANTIHUMAN HEMOLYSIN BY THE COMBINED INTRAPERITONEAL-INTRAVENOUS INJECTION OF INCREASING DOSES OF PLAIN CELLS (AFTER THE METHOD OF BRONFENBRENNER AND SCHLESINGER) EVERY 5 DAYS

PRELIMI- NARY	1 INTRAVEN.	2 INTRAVEN.	1 INTRAPERIT. 3 INTRAVEN.	2 INTRAPERIT. 4 INTRAVEN.	3 INTRAPERIT. 5 INTRAVEN.
—*	—	1:16	1:60	Died	
—	—	1:10	1:20	Died	
—	—	1:25	1:50	1:110	Died
—	—	—	1:20 (Died)		
—	—	1:20	1:40	1:60	1:80
—	—	1:12	1:20	1:60	1:90

*— = less than 1:10.

TABLE VII

THE PRODUCTION OF ANTIHUMAN HEMOLYSIN BY THE SUBCUTANEOUS INJECTION
OF 2 C.C. WASHED PLAIN AND SENSITIZED CELLS EVERY 5 DAYS

CORPUS- CLES	PRELIMI- NARY	1 INJECTION	2 INJECTIONS	3 INJECTIONS	5 INJECTIONS	6 INJECTIONS
Plain	—*	—	—	—	Died	
"	—	—	—	—	1:10	Died
"	—	—	—	—	1:20	1:60 Died
"	—	—	—	1:10	1:18	1:30
Sensitized	—	—	—	—	Died	
"	—	—	—	—	1:10	1:40

*— = less than 1:10.

TABLE VIII

THE PRODUCTION OF ANTIHUMAN HEMOLYSIN BY THE INTRAPERITONEAL INJECTION
OF 5 C.C. OF PLAIN WASHED CELLS PER KILOGRAM OF WEIGHT EVERY 7 DAYS

PRELIMI- NARY	2 INJECTIONS	3 INJECTIONS	5 INJECTIONS	6 INJECTIONS	7 INJECTIONS	8 INJECTIONS
—*	—	1:10	1:20	1:25	1:70	1:80
—	—	1:10	1:20	1:20	1:25	1:40

*— = less than 1:10.

TABLE IX

THE PRODUCTION OF ANTIHUMAN HEMOLYSIN BY THE INTRAPERITONEAL INJECTION
OF 3 C.C. OF PLAIN WASHED CELLS PER KILOGRAM OF BODY WEIGHT EVERY 3 DAYS

PRELIMI- NARY	3 INJECT.	6 INJECT.	9 INJECT.	11 INJECT.	14 INJECT.	17 INJECT.	19 INJECT.	23 INJECT.
—*	—	1:10	1:14	1:33	1:40	1:40	1:40	1:50
—	—	—	1:10	1:20	1:25	1:40	1:40	1:100

*— = less than 1:10.

TABLE X

THE PRODUCTION OF ANTIHUMAN HEMOLYSIN BY THE INTRAVENOUS INJECTION OF
10 C.C. OF 10% SOLUTION OF HEMOGLOBIN PER KILOGRAM
OF WEIGHT EVERY 3 DAYS

PRELIMINARY	5 INJECTIONS	6 INJECTIONS	7 INJECTIONS	8 INJECTIONS	10 INJECTIONS	12 INJECTIONS
—*	—	1:10	1:18	Died		
—	—	1:25	1:30	1:25		
—	—	1:10	1:20	0	1:30	1:60
				1:40	1:40	1:50

*— = less than 1:10.

TABLE XI

THE PRODUCTION OF ANTIHUMAN AGGLUTININ BY THE INTRAVENOUS INJECTION OF 2 C.C. PLAIN WASHED CELLS PER KILOGRAM OF WEIGHT EVERY 5 DAYS (NOGUCHI)

PRELIMI- NARY	1 IN- JECTION	2 IN- JECTIONS	3 IN- JECTIONS	4 IN- JECTIONS	5 IN- JECTIONS	6 IN- JECTIONS	7 IN- JECTIONS
—*	1:10	1:50	1:100	1:150	1:300	Died	0
—	—	1:60	1:100	1:125	1:200	1:400	1:450
—	1:10	1:40	1:90	1:100	1:200	1:300	Died
—	1:10	1:60	1:200	1:300	Died	0	0
—	1:10	1:40	1:80	1:200	1:250	1:300	1:400
—	—	1:30	1:100	1:300	Died	0	0

*—= no agglutination 1:10.

TABLE XII

THE PRODUCTION OF ANTIHUMAN AGGLUTININ BY THE INTRAPERITONEAL INJECTION OF INCREASING DOSES OF PLAIN CELLS (AFTER THE METHOD OF NOGUCHI) AND OF SENSITIZED CELLS EVERY 5 DAYS

CORPUS- CLES	PRELIMI- NARY	1 INJECT.	3 INJECT.	4 INJECT.	5 INJECT.	6 INJECT.	7 INJECT.	8 INJECT.
Plain	—*	1:25	1:100	1:300	1:400	1:400	Died	
"	—	1:25	1:50	Died				
"	—	1:25	1:50	Died				
"	—	1:100	1:125	1:250	1:600	Died		
"	—	1:10	1:200	1:500	1:500	Died		
"	—	1:20	1:150	1:300	1:500	1:500	1:600	1:800
"	—	1:10	1:50	1:200	1:400	1:500	Died	
"	—	1:20	1:30	1:100	1:200	1:400	1:500	1:800
Sensitized	—	1:10	1:50	Died				
"	—	1:50	1:100	1:250	1:250	1:500	Died	
"	—	1:10	1:40	1:90	1:200	1:300	1:500	Died
"	—	1:10	1:50	1:200	1:300	1:450	1:800	1:800
"	—	1:20	1:100	1:100	1:400	1:500	1:600	1:700
"	—	1:10	1:80	1:120	1:300	1:400	1:500	Died

*—= less than 1:10.

TABLE XIII

THE PRODUCTION OF ANTIHUMAN AGGLUTININ BY THE DAILY INTRAVENOUS INJECTION OF 0.1 C.C. WASHED PLAIN CELLS PER KILOGRAM OF WEIGHT (COCA-THOMPSON METHOD)

PRELIMI- NARY	4 INJECT.	8 INJECT.	11 INJECT.	15 INJECT.	18 INJECT.	21 INJECT.	32 INJECT.
—*	1:10	1:25	1:100	1:200	1:600	1:500	
—	—	1:50	1:60	1:300	1:400	1:400	
—	1:10	1:50	1:60	1:250	Died		
—	1:10	1:60	1:60	Died			
—	—	1:25	1:50	1:150	1:200	1:300	1:800
—	—	—	1:10	1:80	1:120	1:200	

*—=no agglutination or incomplete hemolysis in 1:10.

TABLE XIV

THE PRODUCTION OF ANTHUMAN AGGLUTININ BY THE INTRAVENOUS INJECTION OF
0.5 C.C. WASHED PLAIN CELLS PER KILOGRAM OF WEIGHT
EVERY OTHER DAY (AFTER THE METHOD OF CRAIG)

PRELIMI- NARY	3 INJECT.	4 INJECT.	6 INJECT.	7 INJECT.	9 INJECT.	10 INJECT.	12 INJECT.
—*	1:25	1:50	1:200	1:400	1:600	Convul- sions	Convul- sions 1:1200
—	1:25	1:50	1:100	1:400	1:500	1:1000	
—	1:25	1:50	Died				
—	1:25	1:50	1:150	Died			
—	1:10	1:25	1:50	1:70	1:80	Died	
—	—	1:25	Died				

*— = less than 1:10.

TABLE XV

THE PRODUCTION OF ANTHUMAN AGGLUTININ BY THE INTRAVENOUS INJECTION OF
0.2 TO 1.5 C.C. PLAIN WASHED CELLS EVERY 7 DAYS (VEDDER)

PRELIMI- NARY	1 INJECTION	2 INJECTIONS	3 INJECTIONS	4 INJECTIONS	5 INJECTIONS	7 INJECTIONS
—*	1:10	1:200	1:200	1:300	1:400	1:500
—	1:10	1:80	1:100	Died	0	0
—	—	1:20	1:80	1:100	1:200	1:300
—	1:10	1:100	1:200	1:250	1:400	1:500
—	1:10	Died	0	0	0	0
—	1:10	1:100	1:150	1:200	1:300	Died

*— = less than 1:10.

TABLE XVI

THE PRODUCTION OF ANTHUMAN AGGLUTININ BY THE COMBINED INTRAPERITONEAL-
INTRAVENOUS INJECTION OF INCREASING DOSES OF PLAIN CELLS (AFTER
THE METHOD OF BRONFENBRENNER AND SCHLESINGER) EVERY 5 DAYS

PRELIMI- NARY	1 INTRA- VENOUS	2 INTRA- VENOUS	1 INTRAPERI- TONEAL 3 INTRA- VENOUS	2 INTRAPERI- TONEAL 4 INTRA- VENOUS	3 INTRAPERI- TONEAL 5 INTRA- VENOUS
—*	1:10	1:250	1:400	Died	
—	—	1:200	1:200	Died	
—	—	1:200	1:500	1:600	
—	—	1:40	Died		
—	—	1:200	1:200		
—	1:10	1:40	1:150	1:300	1:600
—	1:10	1:60	1:80	1:200	1:350

*— = less than 1:10.

TABLE XVII

THE PRODUCTION OF ANTIHUMAN AGGLUTININ BY THE INTRAVENOUS INJECTION OF 2 C.C. WASHED PLAIN AND SENSITIZED CELLS EVERY 5 DAYS

CORPUS- CLES	PRELIMI- NARY	1 INJECTION	2 INJECTIONS	3 INJECTIONS	5 INJECTIONS	6 INJECTIONS
Plain	—*	—	1:50	1:100	Died	
"	—	—	1:25	1:100	1:200	Died
"	—	—	1:25	1:40	1:90	1:120
"	—	—	1:10	1:30	1:80	1:200
Sensitized	—	—	1:10	1:60	Died	
"	—	—	1:10	1:30	1:80	1:100

*— = less than 1:10.

TABLE XVIII

THE PRODUCTION OF ANTIHUMAN AGGLUTININ BY THE INTRAPERITONEAL INJECTION OF 5 C.C. OF PLAIN WASHED CELLS PER KILOGRAM OF WEIGHT EVERY 7 DAYS

PRELIMI- NARY	2 INJECTIONS	3 INJECTIONS	5 INJECTIONS	6 INJECTIONS	7 INJECTIONS	8 INJECTIONS
—*	—	1:10	1:25	1:40	1:130	1:200
—	—	1:10	1:12	1:40	1:100	1:200

*— = less than 1:10.

TABLE XIX

THE PRODUCTION OF ANTIHUMAN AGGLUTININ BY THE INTRAPERITONEAL INJECTION OF 3 C.C. OF PLAIN WASHED CELLS PER KILOGRAM OF BODY WEIGHT EVERY 3 DAYS

PRELIMI- NARY	3 INJECT.	6 INJECT.	9 INJECT.	11 INJECT.	14 INJECT.	17 INJECT.	19 INJECT.	23 INJECT.
—*	—	—	1:100	1:120	1:200	1:400	1:200	1:800
—	—	—	1:100	1:110	1:120	1:400	1:800	1:500

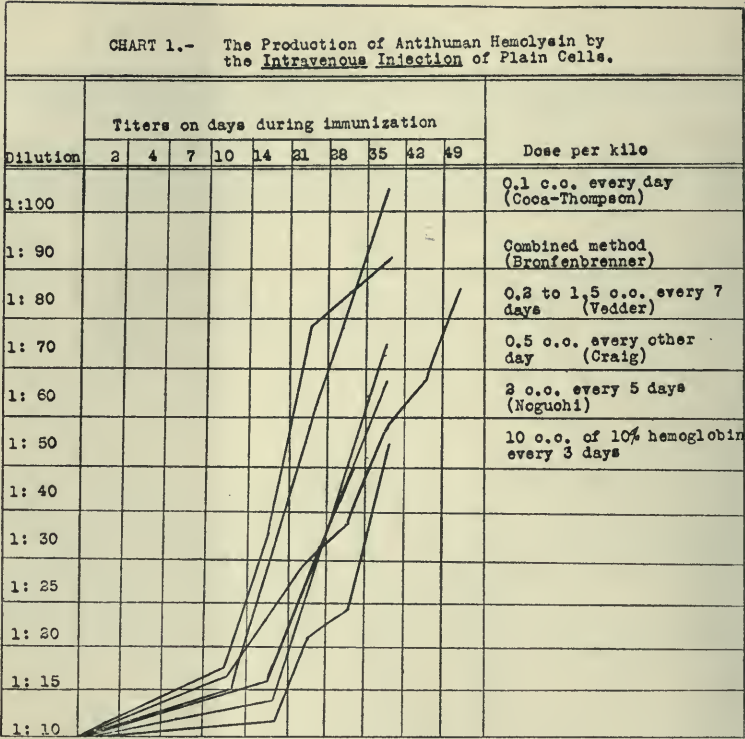
*— = less than 1:10.

TABLE XX

THE PRODUCTION OF ANTIHUMAN AGGLUTININ BY THE INTRAVENOUS INJECTION OF 10 C.C. OF 10% SOLUTION OF HEMOGLOBIN PER KILOGRAM OF WEIGHT

PRELIMI- NARY	5 INJECTIONS	6 INJECTIONS	7 INJECTIONS	8 INJECTIONS	10 INJECTIONS	12 INJECTIONS
—*	—	1:50	1:120	Died 1:150		
—	1:12	1:60	1:200	0	1:400	1:500
—	—	1:50	1:120	1:200	1:400	1:600

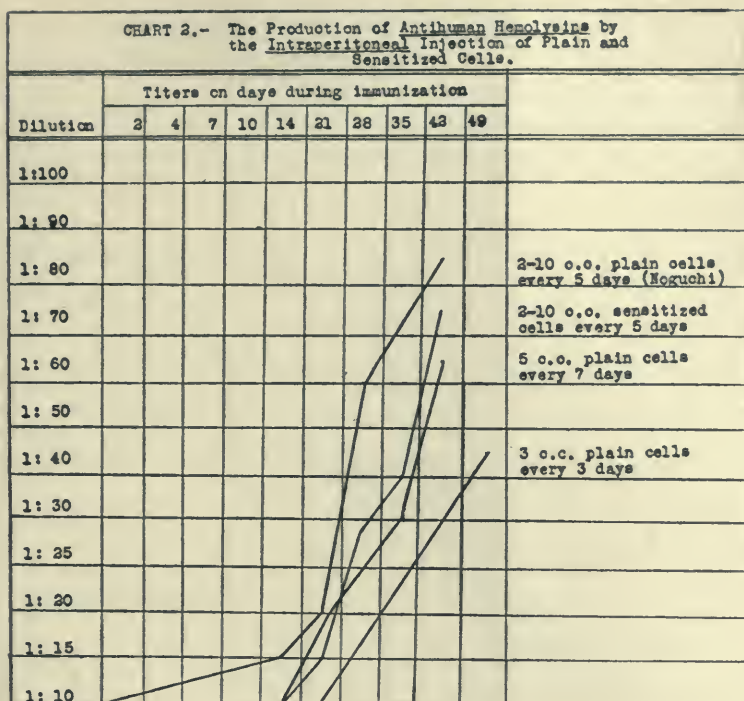
*— = less than 1:10.



Curves of hemolysin production plotted on the basis of averages are shown in Charts 1 and 2; the curves of agglutinin production are shown in Charts 3 and 4. In these charts the curves of antibody production during the first week or ten days are diagrammatic and represented in straight lines inasmuch as daily titrations were not conducted except in the Thompson method; the end results, however, are expressed in a satisfactory manner and show at a glance the general results secured with the different methods used in this investigation.

The general results are summarized as follows:

- (a) As a general rule intravenous methods were superior to intraperitoneal, inasmuch as hemolysin production occurred more quickly, required fewer injections, and smaller doses of cells; otherwise the end results were quite similar.
- (b) Best results were secured in the production of hemolysin by



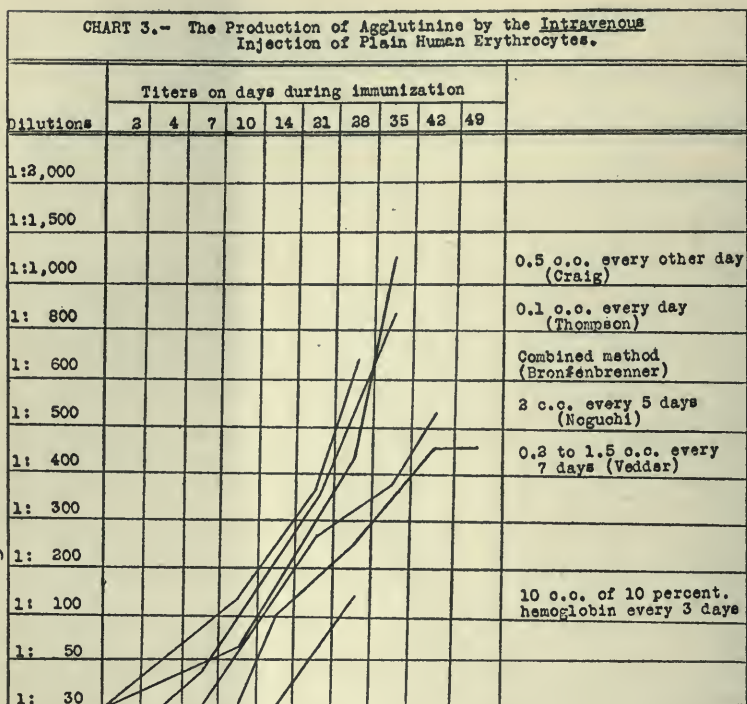
the daily intravenous injection of 0.1 c.c. of cells after the method of Thompson. During the first week hemolysin production is slight and rabbits generally require three to four weeks of immunization before the sera are satisfactory.

(c) The methods of Bronfenbrenner and Schlesinger, Vedder, Craig and Noguchi yielded similar results and no regular relations could be worked out between the doses and intervals of injection with antibody production.

(d) A filtered solution of cells in distilled water proved inferior in antigenic activity to whole cells.

(e) Sensitized cells produced somewhat less hemolysin but more agglutinin than plain cells; as shown later with the sheep cell series, however, sensitized cells have occasionally produced hemolysin somewhat more promptly than plain cells.

(f) Hemolysin and agglutinin production were roughly parallel; as a general rule both antibodies were produced simultaneously,

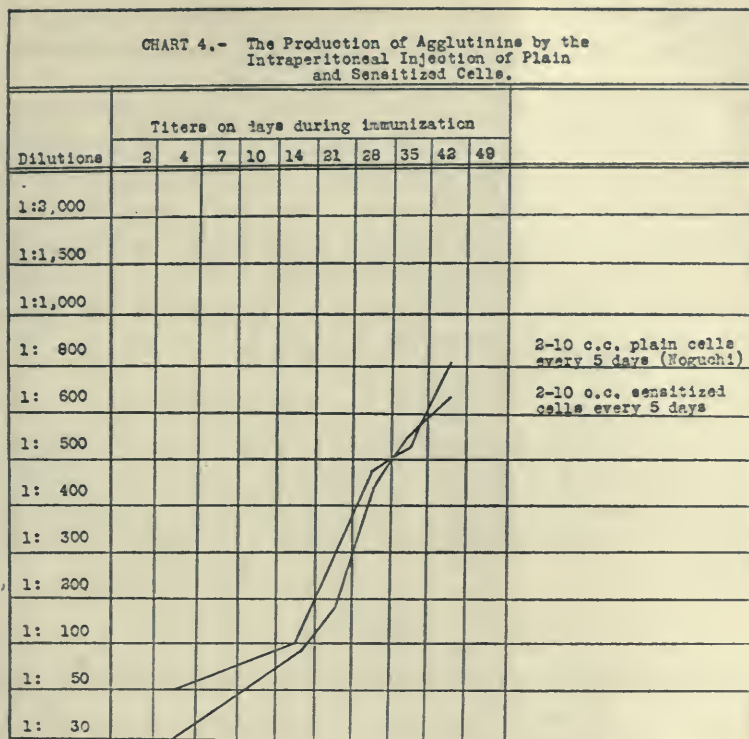


although hemolysin production appears to outstrip agglutinin production with prolonged immunization. An average of our results shows that sera with a hemolytic unit of 1:80 in the technic employed, agglutinated in dilutions of about 1:500.

2. *The Toxicity of Human Cells.*—Undoubtedly human cells are highly toxic for rabbits and either antibody production is suppressed or the antibody producing tissues of the rabbit are poorly responsive to the antigenic activity of the human erythrocytes.

All of the animals lost in weight; those receiving intraperitoneal injections lost less rapidly than those receiving intravenous injections, but even the subcutaneous injection of human cells is followed by gradual reduction in weight.

The death rate among the animals was high; with the Thompson method of daily injections of a small dose of cells we lost about 30 per cent of animals. With the other intravenous methods we lost from 50 to 75 per cent of animals before the sera were suffi-



ciently hemolytic for bleeding. With the intraperitoneal method the death rate was somewhat less. The majority of our animals died one to three days after an injection of cells and less than 5 per cent succumbed during or immediately after the injections with symptoms and postmortem lesions of anaphylactic shock.

Part 3

PRODUCTION OF HEMOLYSINS FOR CHICKEN, GUINEA PIG, RAT AND BEEF ERYTHROCYTES

Additional experiments have been conducted in the preparation of hemolysins for chicken, guinea pig, rat, and beef corpuscles consisting in the intravenous injection of rabbits with the respective cells washed very thoroughly, in dose of 1 c.c. of packed corpuscles suspended in 4 c.c. of salt solution per kilo of body weight every five

days. The main object was to determine the ease or difficulty with which these hemolysins could be produced by the immunization of rabbits.

The results may be summarized as follows: rabbits reacted to injections of chicken, guinea pig, and rat corpuscles in much the same manner as to human cells, that is, hemolysin production was tardy and never marked, agglutinin production was prompt and marked and the death rate among the animals was high; with beef cells the results were similar to those following the injection of sheep corpuscles, that is, hemolysin production was prompt and reached a high degree, agglutinin production was slow and in slight degree and the death rate low.

For the production of antichickens hemolysin, we have secured best results with the daily intravenous injection of 0.1 c.c. washed cells suspended in 1 c.c. sterile salt solution; to remove the necessity of securing fresh blood every day, our corpuscles were kept in a refrigerator in 1:800 formalin in isotonic salt solution for about two weeks.

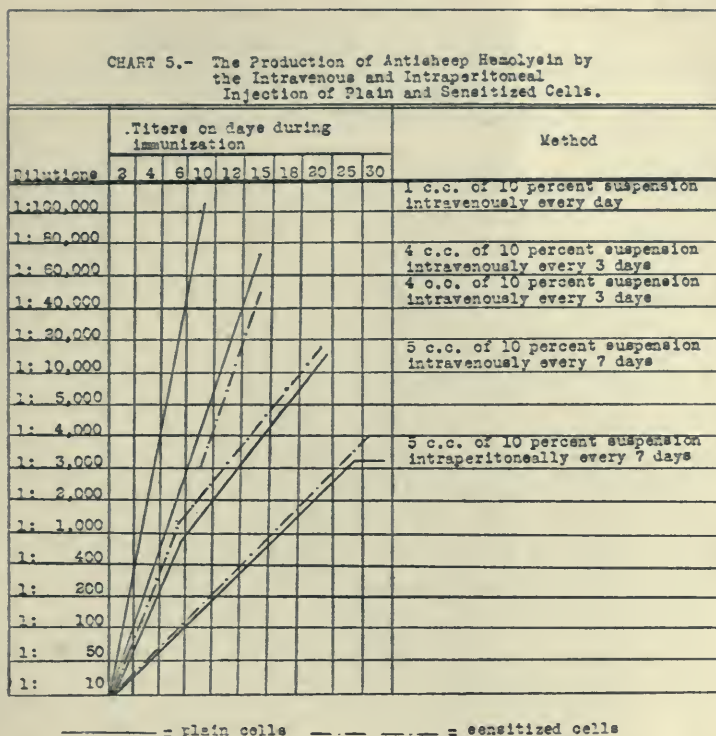
Part 4

METHODS EMPLOYED FOR THE PRODUCTION OF ANTISHEEP HEMOLYSIN

The production of antisheep hemolysin in rabbits is so simple and easy as compared with the production of antihuman that the subject has not attracted much attention; practically any method devised along generally accepted lines and with proper attention to the usual technical details will yield a satisfactory serum. Sheep cells are but slightly toxic for rabbits, and the antibody producing tissues are promptly and powerfully influenced so that the majority of animals survive and produce highly potent immune sera. Agglutinin production for sheep cells is tardy and never reaches a high degree as compared with hemolysin production; no serologist of experience should consent to use any but highly potent sera in view of the ease of production, and no laboratory should be without the simple means of providing an adequate supply of this hemolysin.

Of the large number of methods advocated for the production of antisheep hemolysin, mention may be made of the following:

In the Hygienic Laboratory, Neill¹⁷ injects rabbits intravenously with 1 c.c. of fresh sheep cells every three days for four injections and tests the serum five days after the last injection; he also injects



intravenously 1 c.c., 1 c.c., and 2 c.c. washed cells on three successive days with a second series of injections after an interval of five days after the method of Gay and Fitzgerald.¹⁸

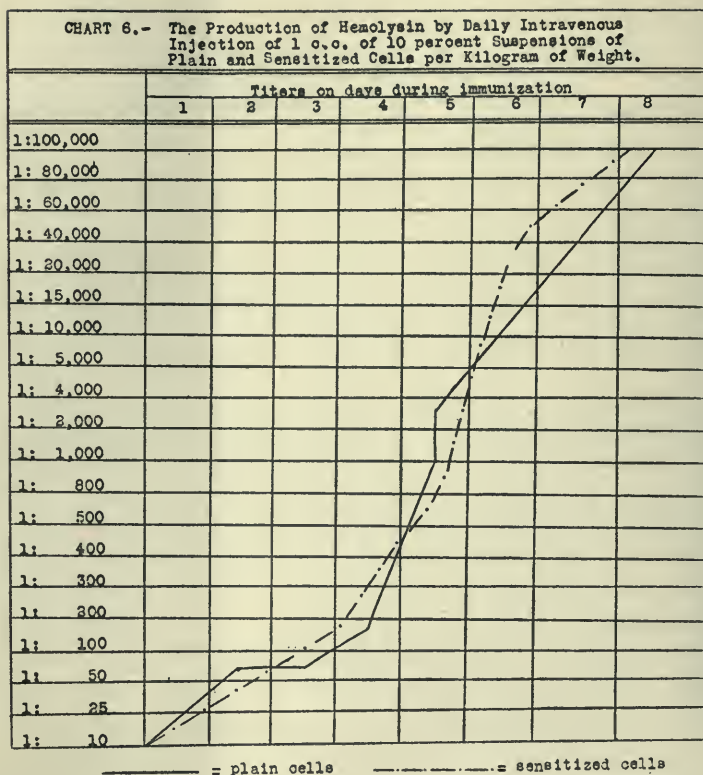
Schweitzer and Stevens¹⁹ in the New York Department of Health Laboratories inject 0.25 c.c. of a fifty per cent suspension of washed cells every three days, increasing the dose by 0.25 c.c. with each injection until four to eight injections have been given.

Coca²⁰ has advocated the daily administration of small doses of cells over a period of several weeks.

One of us (Kolmer) has used for several years an intravenous method consisting in the injection of 5 c.c. of a 10 per cent suspension of washed cells every three days until four injections have been given.

In this investigation plain and sensitized cells were employed for the immunization of rabbits after the following scheme:

1. The *daily intravenous* injection of 1 c.c. of a 10 per cent sus-



pension per kilogram of weight; this is equivalent to 0.1 c.c. undiluted cells, and the method is after that of Coca.

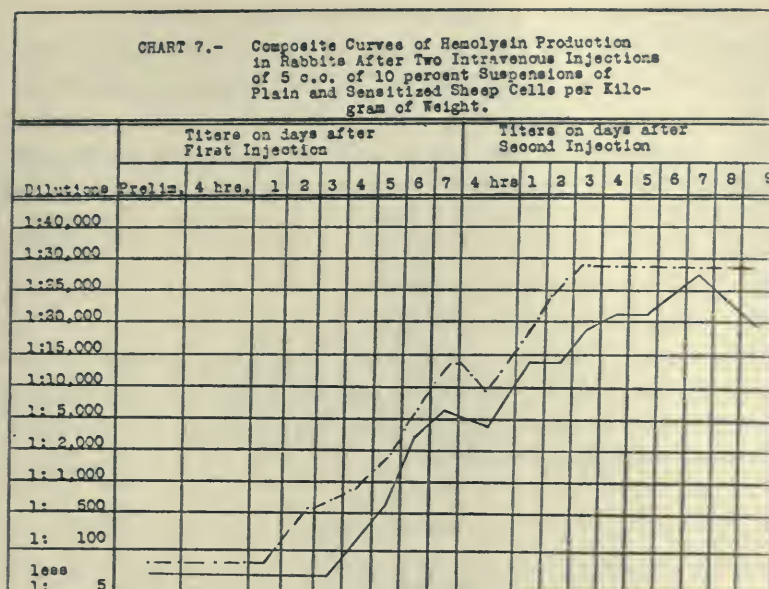
2. The *intravenous injection* of 4 c.c. of a 10 per cent suspension per kilogram of weight every three days.

3. The *intravenous injection* of 5 c.c. of a 10 per cent suspension per kilogram of weight every seven days.

4. The *intravenous injection* of 4 c.c. of a filtered 10 per cent solution of cells in distilled water per kilogram of weight every three days.

5. The *intraperitoneal injection* of 5 c.c. of a 10 per cent suspension per kilogram of weight every seven days.

6. The *subcutaneous injection* of 1 c.c. of a 10 per cent suspension per kilogram of weight every four days.



———— = injection of plain cells
 - - - - - = injection of sensitized cells

RESULTS OF IMMUNIZATION WITH SHEEP CELLS

1. *The Production of Hemolysins.*—The results of hemolysin production by these methods shown in Tables XXI to XXVII and graphically in Charts 5, 6, and 7, may be summarized as follows:

(A) Intraperitoneal and subcutaneous injections were decidedly inferior to intravenous methods for the production of antisheep hemolysin (Tables XXV and XXVI); longer periods of time were required for the production of hemolysins by the usual intraperitoneal technic and a larger percentage of animals succumbed during the process of immunization.

(B) The daily intravenous injection of a small dose of cells, namely, 1 c.c. of a 10 per cent suspension per kilogram of weight yielded the best results in this series (Table XXI, Charts 5 and 6). Next best results were secured with the intravenous injection of 4 c.c. of a 10 per cent suspension per kilogram of weight every three days for four or five injections (Table XXII).

(C) The intravenous injection of a filtered 10 per cent solution

of washed sheep cells in distilled water (Table XXIV) proved less antigenic than corresponding doses of whole cells (Table XXII).

(D) The sera of a proportion of rabbits contained natural anti-sheep hemolysin as previously described²¹ and not infrequently these animals appeared to react more promptly and yield more immune hemolysin than other animals receiving the same amount of sheep cells per kilogram of weight but without natural hemolysins in their sera.

(E) Immunization with sensitized cells yielded results quite similar to those observed with plain cells (Charts 6 and 7). With some animals hemolysin production appeared somewhat more promptly after injections of sensitized cells, but not regularly, and the end results were practically identical, allowing for the marked individual variation of rabbits.

TABLE XXI

PRODUCTION OF ANTISHEEP HEMOLYSIN BY INTRAVENOUS INJECTIONS OF PLAIN AND SENSITIZED CELLS EVERY DAY IN DOSE OF 1 C.C. OF 10% SUSPENSION PER KILOGRAM OF WEIGHT

CORPUSCLES	HEMOLYTIC UNITS OF SERA AFTER INJECTION							
	PRELIMI-NARY	2	3	4	5	6	7	8
Plain	1:10	1:50	1:50	1:30	1:4000	1:10,000	1:50,000	1:100,000
"	-	1:90	1:90	1:250	1:2000	1:10,000	1:30,000	1:100,000
Sensitized	-	-	-	1:80	1:500	1:3,000	1:10,000	1:100,000
"	-	1:50	1:200	1:500	1:2000	1:10,000	1:25,000	1:100,000

TABLE XXII

PRODUCTION OF ANTISHEEP HEMOLYSIN BY INTRAVENOUS INJECTIONS OF PLAIN AND SENSITIZED CELLS EVERY THREE DAYS IN DOSE OF 4 C.C. OF 10% SUSPENSION PER KILOGRAM OF WEIGHT

CORPUSCLES	HEMOLYTIC UNITS OF SERA AFTER INJECTION				
	PRELIMI-NARY	2	3	4	5
Plain	1:10	1:50	1:2500	1:25,000	1:62,000
"	1:20	1:25	1:2500	1:25,000	1:80,000
Sensitized	-	-	1:2500	1:30,000	1:40,000
"	1:10	1:50	1:3000	1:35,000	1:50,000

TABLE XXIII

PRODUCTION OF ANTISHEEP HEMOLYSIN BY INTRAVENOUS INJECTIONS OF PLAIN AND SENSITIZED CELLS ONCE A WEEK IN DOSE OF 5 C.C. OF 10% SUSPENSION PER KILOGRAM OF BODY WEIGHT

CORPUSCLES	HEMOLYTIC UNITS OF SERA			
	PRELIMINARY	1	2	3
Plain	1:10	1:1000	1:3000	1:16,000
Plain	1:10	1:800	1:5000	1:10,000
Sensitized	1:20	1:1200	1:5000	1:20,000
Sensitized	1:10	1:600	1:2500	1:10,000

TABLE XXIV

PRODUCTION OF ANTISHEEP HEMOLYSIN BY INTRAVENOUS INJECTION OF A 10% SOLUTION OF HEMOGLOBIN PER KILOGRAM OF BODY WEIGHT EVERY THREE DAYS

HEMOLYTIC UNITS OF SERA AFTER INJECTIONS				
PRELIMINARY	2	3	4	5
1:12	1:250	1:500	1:3,000	1:18,000
-	-	1:500	1:4,000	1:11,000

TABLE XXV

PRODUCTION OF ANTISHEEP HEMOLYSIN BY INTRAPERITONEAL INJECTION OF PLAIN AND SENSITIZED CELLS ONCE A WEEK IN DOSE OF 5 C.C. OF 10% SUSPENSION PER KILOGRAM OF BODY WEIGHT

CORPUSCLES	HEMOLYTIC UNITS OF SERA AFTER INJECTIONS					
	PRELIMINARY	2	3	4	5	6
Plain	1:10	1:300	1:2000	1:2500	1:3000	1:3000
Plain	-	1:500	Died			
Plain	-	1:250	1:1600	1:1000	Died	
Plain	1:10	1:250	1:2500	1:700	1:3000	1:3000
Sensitized	1:25	1:350	1:2000	1:2200	1:2800	1:3000
Sensitized	-	1:1000	1:1000	Died		
Sensitized	-	1:160	1:2500	1:700	1:3000	1:3400
Sensitized	-	1:160	1:1250	Died		

TABLE XXVI

PRODUCTION OF ANTISHEEP HEMOLYSIN BY SUBCUTANEOUS INJECTION OF PLAIN AND SENSITIZED CELLS EVERY FOUR DAYS IN DOSE OF 1 C.C. OF 10% SUSPENSION PER KILOGRAM OF WEIGHT

CORPUSCLES	HEMOLYTIC UNITS OF SERA AFTER INJECTION										
	PRELIM.	2	3	4	5	6	7	8	9	10	11
Plain	1:10	1:25	1:50	1:500	1:2500	1:1500	1:750	1:900	1:2500	1:1400	1:7000
Sensitized	-	-	-	1:130	1:500	1:1250	1:700	1:1000	Died		
Sensitized	-	-	-	1:40	1:250	Died					

TABLE XXVII
RAPIDITY OF HEMOLYSIN PRODUCTION AFTER VARIOUS METHODS OF IMMUNIZATION

DOS PER KILOGRAM	INJECTION	SHEEP CELLS	Prelim. tests	TITERS AFTER FIRST INJECTION							TITERS AFTER SECOND INJECTION						DAYS			
			DAYS																	
				4 hrs.	1	2	3	4	5	6	7	4 hrs.	1	2	3	4	5	7	9		
5 c.c. 10% suspension	Intraven	Plain	*	-	-	-	-	0	1:500	1:2500	1:5000	1:4000	1:10000	1:8000	1:5000	0	1:5000	1:15000	1:15000		
5 c.c. 10% suspension	Intraven	Sensitized	-	-	-	-	-	0	1:2500	1:10000	1:10000	1:16000	1:2500	1:40000	1:40000	0	1:40000	1:40000	1:40000		
10 c.c. 50% suspension	Intraven	Plain	-	-	-	-	-	0	1:500	1:1600	1:2500	1:5000	1:12000	0	1:15000	0	1:15000	1:25000	1:25000		
10 c.c. 50% suspension	Intraven	Sensitized	-	0	1:5	1:50	† 1:100					1:50	1:1000	1:2500	1:5000	1:10000	0	1:12000	1:12000		
5 c.c. 10% suspension	Intrapert	Plain	-	-	-	-	-	0	1:500	1:500	1:3000	1:4000	1:5000	1:10000	1:13000	1:13000	0	1:15000	1:15000		
5 c.c. 10% suspension	Intrapert	Sensitized	-	-	-	-	-	0	1:600	1:2500	1:5000	1:4000	1:12000	1:15000	0	1:15000	1:15000	1:15000			
10 c.c. 50% suspension	Intrapert	Plain	-	-	-	-	-	0	1:600	1:5000	1:5000	1:6000	1:5000	1:20000	0	1:25000	1:25000	1:25000			
10 c.c. 50% suspension	Intrapert	Sensitized	-	1:50	1:500	1:500	0	1:1000	Died												

* — = No hemolysis or incomplete hemolysis in 1:5 dilution.

† Given second injection at this time in error. †

TABLE XXVIII
RAPIDITY OF HEMOLYSIN PRODUCTION AFTER VARIOUS METHODS OF IMMUNIZATION

DOSE PER KILO	INJECTION	SHEEP CELLS	FIRST INJECTION				SECOND INJECTION				THIRD INJECTION.....DAYS						
			DAYS				DAYS				4 hrs.						
			4 hrs.	1	2	3	4 hrs.	1	2	3	1	2	3	4	5	7	9
4 c.c. 10% suspension	Intraven.	Plain	—	—	0	—	1:25	1:800	1:3000	1:20000	1:16000	1:25000	1:30000	1:30000	1:40000	1:60000	1:40000
4 c.c. 10% suspension	Intraven.	Sensitized	—	—	—	1:25	0	0	1:400	1:16000	1:4000	1:10000	1:25000	1:20000	0	1:50000	1:20000

TABLE XXIX

THE EFFECT OF HEAT AND PRESERVATION ON ANTISHEEP HEMOLYTIC SERA

No.	PRELIMINARY BLEEDING		FINAL BLEEDING		Serum plus glycerol*	Serum plus tricresol*
	Unheated	Heated	Unheated	Heated		
16	1:50,000	1:32,000	1:100,000	1:50,000	1:50,000	1:50,000
11	1:125,000	1:62,500	1:65,000	1:60,000	1:33,000	1:25,000
7	1:50,000	1:30,000	1:60,000	1:60,000	1:50,000	1:32,000
14	1:25,000	1:20,000	1:50,000	1:32,000	1:30,000	1:30,000
1	1:33,000	1:30,000	1:40,000	1:25,000	1:30,000	1:40,000
4	1:100,000	1:75,000	1:40,000	1:40,000	1:40,000	1:40,000
5	1:30,000	1:30,000	1:40,000	1:35,000	1:80,000	1:62,000
10	1:75,000	1:60,000	1:42,000	1:40,000	1:40,000	1:38,000

*Results of tests one week later.

2. *The Toxicity of Sheep Cells.*—Rabbits withstand injections of sheep cells remarkably well if a careful technic is employed; less than 20 per cent of our animals lost in weight and more than this percentage gained during the process of immunization. Practically none of the animals receiving intravenous injections succumbed, whereas about 40 per cent of those receiving intraperitoneal injections died before the periods of immunization were completed; in two of these there were evidences of peritonitis.

3. *Rapidity of Hemolysin Production.*—In Tables XXVII and XXVIII and Charts 6 and 7 are shown the results of daily titrations of the sera of rabbits receiving daily injections of sheep cells and one injection every seven days; the first serum was secured from each animal about twenty-four hours after receiving an injection of cells.

As shown in Chart 6, animals receiving daily injections of small amounts of blood cells began to produce thermostabile hemolysin within forty-eight hours after receiving the first dose; the single injection of a larger amount of plain cells was followed by the production of thermostabile hemolysin after three days and in forty-eight hours after the administration of sensitized cells (Chart 7).

After one intravenous injection of sheep cells in dose of 5 c.c. of a 10 per cent suspension per kilogram of weight, hemolysin production steadily increased for at least seven days; after this time the titer of the sera either remained about the same or began to drop to a slight extent; four hours after a subsequent injection of cells the titer had dropped slightly followed in twenty-four hours by recovery to the former level and a steady increase.

Part 5

THE COLLECTION AND PRESERVATION OF HEMOLYTIC SERA

1. *The Collection of Sera.*—Most authors advise bleeding an animal four to nine days after the last injection of cells when preliminary titrations conducted with serum secured by collecting blood from an ear vein, have shown that the titer is satisfactory. According to our experiments the best time for bleeding appears to be about seven days after the last injection by the intravenous route, inasmuch as hemolysin production is likely to occur for about this time after an injection of the antigen.

A preliminary titration of serum secured from a small amount of blood from an ear vein may not give an exact idea of the content in hemolysin inasmuch as the serum of the whole blood secured by bleeding the animal to death may show less or slightly more hemolysin; in the majority of our experiments the serum of the whole blood was slightly more hemolytic (Table XXIX).

If the serum is to be preserved dried on paper as appears advisable with antihuman serum or with an equal part of glycerol as appears best for the preservation of antisheep and antiox sera, it is unnecessary to observe elaborate aseptic precautions in the bleeding of an animal; indeed, an attempt to bleed aseptically from a carotid artery is frequently followed by loss of a portion of blood, and the operation may be a failure. We believe that it suffices to exsanguinate rabbits in exactly the same manner as described for the collection of complement serum from guinea pigs,²² namely, severing the vessels of the neck under light anesthesia and collecting the blood in large centrifuge tubes by means of a funnel. After standing several hours the serum may be removed or the clots gently broken up with a rod, and the corpuscle free serum secured by centrifuging; in our experience the presence of some hemoglobin in the serum does not alter its biological properties and is not objectionable except from the standpoint of appearance.

2. *The Preservation of Hemolytic Sera.*—Fresh serum is more hemolytic than heated or aged serum due principally to the presence of thermolabile in addition to thermostable hemolysins; as shown in Table XXIX heating an immune serum at 56° C. for one-half hour generally reduces the hemolytic activity due to the destruction of thermolabile hemolysins in addition to the native com-

plements. The addition to unheated serum of an equal part of sterile glycerol or tricesol to the extent of 0.4 per cent is followed within a week by a destruction of the thermolabile hemolysins, reducing the titer to that of the same serum after heating. Most authors advise heating an immune serum before adding a preservative, but in our experience this is unnecessary unless the serum is to be kept without the addition of a preservative, under which conditions heating may serve to sterilize the serum unless spore bearing bacilli have gained access.

A variety of methods have been advocated for the preservation of hemolytic sera including the addition of phenol, tricesol, chloroform, glycerol and drying on special filter paper. For the preservation of antihuman serum we believe that drying on filter paper as advised by Noguchi and employed by the majority of serologists employing the antihuman hemolytic system as Noguchi, Bronfenbrenner, Craig and Vedder, is the preferable method not only because of its convenience and remarkable preservation of the hemolysin, but also by reason of the results of studies by Sands and West¹⁰ in these laboratories, indicating that drying tends to remove a portion of the highly objectionable agglutinins for human erythrocytes.

Phenol, tricesol, and chloroform tend to cloud the sera when used in amounts sufficiently large to prove antiseptic; one of us (J. A. K.) has used for over seven years sterilized glycerol for the preservation of all hemolysins other than antihuman and Clock and Beard²³ have also found glycerol an acceptable preservative for antishoop hemolytic serum. An equal volume of sterile neutral glycerol of the best quality is added to the fresh unheated hemolytic serum and the mixture kept in a refrigerator stored in bulk or in ampules. The proportion of glycerin is antiseptic and the mixtures never become overgrown with bacteria regardless of how frequently they are tapped under ordinary conditions; furthermore the hygroscopic properties of glycerin tends to prevent molecular changes preserving the hemolytic titer of a mixture remarkably constant over a period of at least a year when kept in a refrigerator. With potent sera requiring high dilution this amount of glycerin is neither hemolytic nor anticomplementary and possesses no objectionable qualities from the standpoint of a preservative for hemolysins.

DISCUSSION

A prominent result of this investigation is to show that the production in rabbits of high titer hemolysin for human corpuscles is a difficult procedure; that an antihuman hemolytic system is theoretically ideal for the complement-fixation test is freely admitted, but the usual difficulty encountered in the preparation of the hemolysin constitutes a real drawback in its general adoption. The same may be said of the production of hemolysins for guinea pig, chicken, and rat corpuscles. With sheep and beef corpuscles, however, hemolysin production is a comparatively easy procedure and high titer products are readily secured; why rabbits should show these marked differences in immunity response to these antigens is unknown, but it is significant in this connection to note that rabbits usually have natural hemolysins in their sera for sheep and beef corpuscles, but none for human cells, and it may be that the cells concerned in the production of hemolysins are more susceptible or "tuned up" for reaction to sheep and beef than to human cells. Since a large proportion of the sera of calves and beef contain natural hemolysins for human cells,²⁴ it is suggested that these animals may produce antihuman hemolysin more readily than rabbits and experiments are now being conducted on this phase of the problem.

Human corpuscles are undoubtedly more toxic for rabbits than sheep and beef corpuscles and this contributes to the high mortality among immunized rabbits; for this reason only large healthy animals should be employed and it is advantageous to feed with particular care and permit them to run about in the open air for exercise.

Aside from the toxicity of human corpuscles for rabbits, we believe that a larger proportion of deaths among rabbits are caused by agglutination *in vivo* than by anaphylaxis; an ideal method for the preparation of antihuman hemolysin would be intravenous immunization with that fraction of human corpuscles exciting hemolysin production alone but none of the methods so far advocated serve this purpose. The daily injections of small doses of washed human corpuscles have yielded us the best results; whether this procedure retards agglutination *in vivo* or minimizes its effects is difficult to state.

With intraperitoneal injections of human corpuscles the danger

of agglutination *in vivo* is minimized, but hemolysin production is much slower and the mortality still high due principally to the toxicity of these cells.

Insofar as immunization with sensitized corpuscles is concerned, the slightly superior results observed do not warrant the extra work involved and the use of immune serum; corpuscles exposed *in vitro* to specific agglutinins may not, however, be susceptible to agglutination *in vivo* which would very probably prove advantageous for the production of antihuman hemolysin by the intravenous route of injection.*

SUMMARY

1. In the production of antihuman and antisheep hemolysins in rabbits best results were secured by the intravenous injection of small doses of washed cells at frequent intervals. The intraperitoneal route is slower, yields less hemolysin, and is accompanied by a higher death rate with sheep cells.

2. In a comparative study of methods for the production of antihuman hemolysin in rabbits best results were secured by the method of Thompson consisting of the daily intravenous injection of 0.1 c.c. of washed cells over a period of three to four weeks. The death rate among rabbits so treated was lower than with other methods and the production of hemolysin relatively high.

3. For the production of antisheep hemolysin best results were secured by the daily intravenous injection of 0.1 c.c. washed cells and next best by the intravenous injection of 5 c.c. of a ten per cent suspension every three days for four injections.

4. Human erythrocytes are highly toxic for rabbits, resulting in producing a marked loss in weight during the period of immunization. Fatalities among the immunized rabbits appeared to be caused by agglutination *in vivo* and the high toxicity of human cells rather than by anaphylaxis.

5. Sheep and ox erythrocytes are but slightly toxic for rabbits, and may be employed for the production of powerfully hemolytic sera low in agglutinins; there is slight or no loss in weight of the rabbits and the death rate is low.

6. Hemolysins for guinea pig, chicken, and rat corpuscles are

*Vedder (Jour. Immunology, 1919, iv, 142) has recently shown that this may be true with human corpuscles sensitized for twelve hours with antihuman serum heated at 78-80° C. for one hour to destroy agglutinins and produce agglutinoids.

produced with about the same difficulty as human hemolysins; anti-chicken hemolysin was best prepared by the daily intravenous injection of 0.1 c.c. washed cells suspended in 1 c.c. sterile saline solution.

7. Sensitized erythrocytes did not generally prove superior to plain cells; not infrequently hemolysin production occurred more promptly and progressed somewhat more rapidly after injection of sensitized erythrocytes, but the end results were practically identical with those following immunization with plain cells.

8. The intravenous injection of plain sheep cells is followed in about three to four days by an increase of hemolysins in the serum and increases quite rapidly; with human cells immune hemolysin is not usually demonstrable for at least seven to ten days after single or repeated injections and increases very slowly.

9. For the collection of immune hemolytic sera rabbits should be bled about seven days after the last injection of cells.

10. Antihuman, antisheep, and antiox sera are well preserved by mixing the sera with an equal part of sterile high grade glycerol and keeping in a refrigerator; antihuman hemolysin is also well preserved dried in special filter paper after the method of Noguchi.

We beg to express our thanks to Mr. Joseph Sands and Mr. Lyle West for valuable assistance in the immunization of rabbits with human cells.

Addendum

VEDDER'S NEW METHOD FOR THE PRODUCTION OF ANTIHUMAN HEMOLYSIN

Since the preparation of this paper, Vedder* has described a new method for the production of antihuman hemolysin and publication has been delayed in order to include an account of our experiences with this method which consists of the intravenous injection of rabbits with stroma secured by hemolysis of washed erythrocytes after they had been exposed to illuminating gas, which largely protects the stroma against solution in water. Vedder regards the stroma of erythrocytes as the chief antigenic substance in the production of hemolysins, and discovered the following method for its preparation:

*Vedder, F. B.: The Production of Antihuman Haemolysin, *Jour. Immunology*, 1919, iv, 141-146.

"Fresh red corpuscles are washed in salt solution and packed in the centrifuge, the exact amount being noted. The corpuscles are diluted with an equal volume of 0.85 per cent NaCl solution in a cylinder and placed outside the window where ordinary illuminating gas is allowed to bubble through it freely for fifteen to twenty minutes. At the end of this time the corpuscles will have taken on the characteristic cherry red color. The salt solution is centrifuged off and sufficient distilled water is added to produce hemolysis. This mixture should be left for an hour or so to permit all the hemoglobin to become dissolved out, the stroma then being separated by centrifugation at high speed. About 33 per cent of the volume of the corpuscles should be recovered as yellowish white stroma. The outline of the stroma cells so obtained is perfect under the microscope, and it appeared that by this method the whole stroma is obtained. The carbon monoxide appears to preserve the stroma so that it does not go into solution so readily when washed." This effect of illuminating gas was discovered by accident. The stroma so obtained is diluted with salt solution up to the original volume of the packed corpuscles, and this suspension is used for immunizing rabbits.

Vedder found that 2.5 c.c. of this suspension of stroma per kilo of body weight constituted the minimal lethal dose; satisfactory hemolysins were produced by giving rabbits an intravenous injection of 1 c.c. followed at five day intervals by doses of 2 c.c. Three such injections have proved sufficient to give hemolysin of good titer in the short period of fifteen days in several rabbits.

In our work the stroma was prepared as described above; preliminary experiments in the preparation of stroma from plain and gassed erythrocytes showed a striking difference, the latter yielding a volume of stroma many times that secured after the hemolysis of plain cells.

In order to compare the immunizing properties of stroma alone with the whole cell, three series of rabbits were injected intravenously, one-half of each series receiving 0.5 c.c. stroma per kilo followed at five-day intervals by 1 c.c., and the remaining animals receiving similar doses of plain whole cells from the same blood. Each animal was bled from the ear four days after each injection, and the sera titrated for hemolysin and hemagglutinin as previously described. The results observed with one series are sum-

marized in Tables XXX and XXXI and are representative of the whole.

In our experience it has appeared that hemagglutinins are not produced by the injection of stroma to the same extent as follows the injection of whole cells, and this is decidedly advantageous, while hemolysin production was about equal; furthermore, the death rate was not as high among those animals receiving stroma alone.

At the present time we are giving daily injections of 0.1 c.c. stroma in 1 c.c. of sterile saline solution with better results than observed with the injection of larger doses at the five-day intervals.

TABLE XXX

THE PRODUCTION OF ANTIHUMAN HEMOLYSIS BY THE INTRAVENOUS INJECTION OF STROMA (VEDDER) AND PLAIN CELLS

ANTIGEN	INJECT. 1	INJECT. 2	INJECT. 3	INJECT. 4	INJECT. 5	INJECT. 6
Stroma	trace	1:10	1:20	Died		
Stroma	trace	1:15	1:25	1:40	1:80	1:80
Stroma	trace	1:12	1:60	1:50	1:100	1:100
Stroma	none	1:10	Died			
Stroma	trace	1:8	1:16	1:30	1:80	Died
Plain cells	trace	1:15	1:30	1:30	Died	
Plain cells	none	1:4	1:20	1:20	Died	
Plain cells	trace	1:10	1:40	1:30	1:40	1:100
Plain cells	trace	1:4	1:10	Died		
Plain cells	none	1:4	1:15	1:30	Died	

TABLE XXXI

THE PRODUCTION OF ANTIHUMAN HEMAGGLUTININ BY THE INTRAVENOUS INJECTION OF STROMA (VEDDER) AND PLAIN CELLS

ANTIGEN	INJECT. 1	INJECT. 2	INJECT. 3	INJECT. 4	INJECT. 5	INJECT. 6
Stroma	trace	1:50	1:25	Died		
Stroma	none	1:50	1:25	1:120	1:160	1:170
Stroma	trace	1:50	1:40	1:110	1:160	1:250
Stroma	none	1:20	Died			
Stroma	trace	1:40	1:40	1:100	1:180	Died
Plain cells	none	1:50	1:160	1:400	Died	
Plain cells	none	1:10	1:160	1:400	Died	
Plain cells	trace	1:50	1:240	1:400	1:600	1:600
Plain cells	trace	1:40	1:120	Died		
Plain cells	trace	1:40	1:140	1:200	Died	

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STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. XI

A STUDY OF METHODS FOR ADJUSTING THE HEMOLYTIC SYSTEM WITH SPECIAL REFERENCE TO THE TITRATION OF COMPLEMENT*

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WHILE the results of investigations reviewed and described in a former article¹ have shown that guinea pig serum is best adapted for complement in complement-fixation tests, the amount to employ and the method of adjustment of the hemolytic system are factors of primary importance in relation to the specificity and sensitiveness of complement-fixation tests; these subjects have required a large amount of attention devoted to comparative studies of different methods in order to arrive at conclusions concerning the best method from the standpoint of a standardized complement-fixation technic.

PRINCIPLES INVOLVED

The problem presents two main phases, namely, the "building up" of a hemolytic system and the method for routinely adjusting it for diagnostic tests. The investigator in this field can not but feel great admiration for the work of Bordet, Wassermann, and other pioneers who must have conducted a great deal of research before announcing the relatively simple and highly efficient directions accompanying descriptions of their technic.

In *building up* a hemolytic system it is of prime importance to so adjust the quantities of corpuscles and hemolysin that the complement unit will never fall below a certain minimum; as shown later in this article, the amount or unit of complement required for complete lysis of a given amount of corpuscles may be reduced so greatly by

*Investigation aided by funds accruing from the preparation of arsphenamine.

an excess of powerful hemolysin as to render the unit entirely worthless in complement-fixation tests owing to the anticomplementary effects of antigen and serum alone and the deterioration of complement during the period of primary incubation.

Under ideal conditions the *adjustment of the hemolytic system* must be so conducted as to provide enough complement for these non-specific agencies, a balance for specific fixation by antibodies and antigen, and a means for detecting and even measuring the latter for the purpose of specific diagnosis.

Furthermore, the technic must adjust the variations of hemolytic activity and fixability of the complement, variation in the sensitizing activity of the hemolysin and of resistance of the corpuscles to lysis.

Variation in hemolytic activity of complement, sensitizing activity of hemolysin and resistance of corpuscles are commonly adjusted by using a fixed and arbitrary amount of complement and corpuscles and titrating the hemolysin, as originally advocated by Wassermann and his associates; or, by using fixed and arbitrary amounts of hemolysin and corpuscles and titrating the complement. Many immunologists see no difference in the choice of either method and probably the majority follow the principles of Wassermann's technic, namely, daily titrations of the hemolysin; others claim that there is a difference in favor of the method of daily titrations of complement, and a primary object of this study was to arrive at a conclusion on this important point by an extensive series of comparative tests employing both methods.

In order to allow for the anticomplementary effects of antigen and serum alone, Bordet, and later Wassermann, advocated the use of fixed amounts of complement which provided a considerable excess and probably resulted in reducing the sensitiveness of the reactions; subsequent investigators who titrated the complement, advised the use of but one or two units in order to avoid this excess and thereby increase the sensitiveness of the complement-fixation test. Recently others have sought to render the technic still more delicate by titrating the complement in the presence of antigen or of antigen and a normal serum, in order to make a closer adjustment for the anticomplementary activities of these substances.

Variation in fixability of guinea-pig serum complement is best overcome by using the mixed sera of several animals¹ even though this involves the use of preserved complement over a period of about

two or three weeks in order to avoid waste. Preliminary titration of complement for fixability by mixtures of extract and syphilitic serum is apparently practiced by a few serologists and while this is advisable when the serum of a single animal is used, it is unnecessary with a mixture of sera and does not warrant the extra work and time involved, insofar as complement fixation in syphilis is concerned.

In the titration of complement for hemolytic activity, the kind and duration of incubation exert an important influence upon the results and even the manner of mixing the three ingredients, namely, complement, hemolysin and cells. For example, water-bath incubation aids the hemolytic activity of complement more than thermostat (air) incubation and in setting up the titration, if the cells and hemolysin are mixed together for five minutes or more before the addition of complement there is sufficient time for enough sensitization to occur to influence the results and reduce the unit of complement.

PURPOSES OF INVESTIGATION

The purposes of this investigation were as follows:

1. A brief study of the important question of absolute minimum of complement in relation to the constitution of a hemolytic system.
2. A study of the influence upon complement-fixation tests of complement versus hemolysin titrations for the daily adjustment of the hemolytic system.
3. A comparative study of different methods for the titration of complement.
4. A study of the relation of kind and duration of incubation to the titration of complement for hemolytic activity; also the influence of the manner in which complement, hemolysin and corpuscles are mixed in conducting this titration.
5. The establishment of certain principles for a standardized technic for the titration of complement based upon the results of these investigations.

Part 1

THE ABSOLUTE MINIMUM OF COMPLEMENT

In every hemolytic system the amount of complement employed may be greatly reduced and complete hemolysis obtained by using increasing amounts of hemolysin as shown by Morgenroth and Sachs;³ the converse is also true to even greater degree, that is, an excess of

complement may produce complete lysis with less than the theoretical amount of hemolysin, which has an important bearing upon "building up" of a hemolytic system.⁴ The point of practical importance is that amounts of complement capable of producing complete hemolysis may be too large or too small for use in complement-fixation tests when used with two units of hemolysin, and particularly so when the complement is used in a fixed amount and the hemolysin titrated. As shown in Table I, varying dilutions of complement were used in constant amount of 1 c.c. for titrating an antish sheep hemolysin and employed in complement-fixation tests with two units of hemolysin; the unit of hemolysin became progressively higher as the amount of complement decreased, but the results of complement-fixation tests showed that the 1:10 dilution represented an excess of complement since the degree of fixation was masked by too much hemolysis; dilutions of complement higher than 1:40 represented too small an amount, the available complement being largely or entirely fixed in a nonspecific manner by antigen and serum alone and resulting in inhibition of hemolysis in the serum controls and in tests conducted with normal serum. Similar experiments with an antihuman hemolytic system (Table II) showed that while the unit of hemolysin may be readily obtained with progressive dilutions of complement used in constant dose of 0.1 c.c., the higher dilutions may prove unsatisfactory. However, when the hemolysin is held as a constant and the complement titrated, the higher dilutions of complement may prove as satisfactory as the lower, the only difference being that larger amounts are used while the actual amount of complement in terms of undiluted serum remains about the same, as shown in Table III.

TABLE I

RESULTS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH AN ANTISHEEP HEMOLYTIC SYSTEM ADJUSTED BY USING VARYING DILUTIONS OF COMPLEMENT IN FIXED AMOUNTS WITH TWO UNITS OF TITRATED HEMOLYSIN

FIXED AMOUNT COMPLEMENT	UNIT OF HEMOLYSIN c.c.	SYPH. SERUM		SYPH. SERUM		NORMAL SERUM		NORMAL SERUM	
		Antigen	Control	Antigen	Control	Antigen	Control	Antigen	Control
1 c.c. 1:10	0.05	+	—	—	—	—	—	—	—
1 c.c. 1:20	0.07	++++	—	+++	—	—	—	—	—
1 c.c. 1:30	0.08	++++	—	++++	—	—	—	—	—
1 c.c. 1:40	0.1	++++	—	++++	—	—	—	—	—
1 c.c. 1:60	0.5	++++	+	++++	+	++	+	+	+
1 c.c. 1:80	0.6	++++	++	++++	+	++	+	+	+
1 c.c. 1:120	2.5	++++	++++	++++	++++	++++	++++	++++	++++

*++++ = strongly positive; +++ = moderately positive; ++ = weakly positive; + = very weakly positive.

TABLE II

RESULTS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH AN ANTIHUMAN HEMOLYTIC SYSTEM ADJUSTED BY USING VARYING DILUTIONS OF COMPLEMENT IN FIXED AMOUNTS WITH TWO UNITS OF TITRATED HEMOLYSIN

FIXED AMOUNT COMPLEMENT	UNIT OF HEMOLYSIN c.c.	SYPH. SERUM		SYPH. SERUM		NORMAL SERUM		NORMAL SERUM	
		Antigen	Control	Antigen	Control	Antigen	Control	Antigen	Control
0.1c.c. 1:1½	0.15	++++	—	++++	—	—	—	—	—
0.1c.c. 1:5	0.25	++++	+	++++	—	+	—	++	+++
0.1c.c. 1:10	0.3	++++	++++	++++	++++	+++	+++	++++	++++
0.1c.c. 1:15	more than 2.0	0	0	0	0	0	0	0	0

TABLE III

RESULTS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH AN ANTIHUMAN HEMOLYTIC SYSTEM ADJUSTED BY USING A FIXED AMOUNT OF HEMOLYSIN WITH TWO UNITS OF COMPLEMENT TITRATED IN VARYING DILUTIONS

UNIT OF COMPLEMENT	EQUIVALENT UNDILUTED SERUM c.c.	SYPH. SERUM		SYPH. SERUM		NORMAL SERUM		NORMAL SERUM	
		Antigen	Control	Antigen	Control	Antigen	Control	Antigen	Control
0.02c.c. 1:1½	0.013	++++	—	+++	—	—	—	—	—
0.03c.c. 1:3	0.009	++++	—	++++	—	—	—	—	—
0.04c.c. 1:5	0.008	++++	—	++++	—	—	—	—	—
0.05c.c. 1:7	0.007	++++	—	++++	—	—	—	—	—
0.08c.c. 1:10	0.008	++++	+	++++	—	—	—	—	—

Without further discussion of this intricate and important subject, upon which a large amount of experimental data is to be found in literature, we wish simply to emphasize the practical difficulties encountered in building up an acceptable hemolytic system, the necessity for so adjusting the amounts of corpuscles and hemolysin that the average unit of complement will fall within a range neither too large nor too small and that from this standpoint the hemolytic system is better adjusted by using the hemolysin as a constant and making daily titrations of complement than the converse.

Part 2

COMPLEMENT VS. HEMOLYSIN TITRATIONS FOR THE DAILY ADJUSTMENT OF THE HEMOLYTIC SYSTEM

As previously stated, Wassermann instituted the method of using complement in a fixed amount (0.1 c.c.) and titrating the hemolysin for the purpose of adjusting an antisheep hemolytic system; this method is still used by Citron, Bruck, Sachs, Kolmer and numerous others in Europe and America, including Noguchi, who adopted the principle for the adjustment of an antihuman hemolytic system. An increasing number of others, however, including Thomsen, Boas,

MacIntosh and Fields, Thomas and Ivy, Walker and Swift, Neill (Hygienic Laboratory) and Ottenberg, have adopted a method of adjusting an antish sheep hemolytic system by titrating the complement instead of hemolysin and both Craig and Vedder are using this method in adjusting an antihuman hemolytic system widely employed in army laboratories. Ottenberg and Frazier⁵ have reported experiments showing that more delicate results in complement-fixation are observed by titrating the complement than by titrating the hemolysin, and in their opinion the correct method for compensating for complements of greater than average hemolytic strength, is by using a smaller dose of complement.

As a matter of fact a great deal of work has been required to settle the point for us and especially so when comparative tests were made with single doses of patients' serum as 0.1 or 0.2 c.c.; differences were, however, brought out by using each serum in graded amounts.

Technic.—In order to render the tests strictly comparative the same complement serum (mixed sera of three or more guinea-pigs) hemolysin, corpuscles, antigen (cholesterolized heart extract) and sera were used in each experiment; one set of tests were conducted with a fixed amount of complement (1 c.c. of 1:20 dilution) and two units of hemolysin titrated against this complement and 1 c.c. of 2.5 per cent suspension of sheep cells with water bath incubation of one hour. In the second series, two units of the hemolysin titrated in this manner were taken as a fixed dose and the complement titrated for the smallest lytic dose and designated as a unit. The sera were heated and used in graded amounts. The primary and secondary incubations were of one hour in a water-bath and the readings made after the tubes had stood in a refrigerator over night.

Results.—In the experiment shown in Table IV the unit of hemolysin was 0.06 c.c. of 1:300 dilution and under "Method A" are shown the results of tests with twelve sera used in amounts varying from 0.1 to 0.00001 c.c. conducted with 1 c.c. of 1:20 complement and two units of hemolysin; the unit of complement as determined with two units of hemolysin was 0.4 c.c. of 1:20 and under "Method B" are shown the results of tests conducted with one unit of complement and two units of hemolysin and under "Method C," the same technic except that two units of complement were employed.

As shown in this table one unit of complement with two units of hemolysin (Method B) did not furnish sufficient complement for the

TABLE IV
COMPLEMENT VERSUS HEMOLYSIN TITRATION AND INFLUENCE UPON COMPLEMENT-FIXATION TESTS

SERA	METHOD A *						METHOD B						METHOD C					
	0.1	10.0	100.0	1000.0	10000.0	0.1 S. C.	0.1	10.0	100.0	1000.0	10000.0	0.1 S. C.	1.0	10.0	100.0	1000.0	10000.0	0.1 S. C.
Syphilitic	4	4	4	1	1	-	4	4	4	4	4	2	4	4	4	4	1	-
Syphilitic	4	4	1	1	-	-	4	4	4	3	1	4	4	4	1	-	-	-
Syphilitic	4	4	1	-	-	-	4	4	4	4	3	1	4	4	4	-	-	-
Syphilitic	2	1	2	-	-	-	4	4	3	2	1	4	4	1	-	1	-	-
Syphilitic	4	4	3	-	-	-	4	4	2	2	-	4	4	4	1	-	-	-
Syphilitic	4	4	2	-	-	-	4	4	4	4	1	1	4	4	3	1	-	-
Syphilitic	4	4	3	-	-	-	4	4	4	2	1	3	4	4	3	-	-	-
Syphilitic	4	4	4	-	-	-	4	4	4	4	1	3	4	4	4	1	-	-
Syphilitic	1	4	4	-	-	1	3	3	2	1	1	3	1	1	4	2	-	-
Nonsyphilitic	-	-	-	-	-	-	1	1	4	4	-	-	-	-	-	-	-	-
Nonsyphilitic	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-	-	-	-

*Method A.—Complement used in fixed amount of 1 c.c. of 1:20; hemolysin titrated and used in two units.
Method B.—Complement titrated with two units of hemolysin and used in dose of one unit with two units of hemolysin.
Method C.—Same as B except that two units of complement were employed.

anticomplementary effects of antigen and serum and proved unsatisfactory. As between the set conducted with titrated hemolysin (Method A) and titrated complement (Method C) the latter proved the more sensitive and yielded positive reactions with smaller amounts of several of the sera.

The results of a similar experiment conducted with fifteen sera used in amounts from 0.2 to 0.006 c.c. are shown in Table V with the same general results, namely, tests conducted with two units of titrated complement were more delicate and sensitive than tests conducted with a constant amount of complement and two units of titrated hemolysin.

TABLE V
COMPLEMENT VERSUS HEMOLYSIN TITRATIONS AND INFLUENCE UPON
COMPLEMENT-FIXATION TESTS

SERA	COMPLEMENT TITRATED; SERUM DOSES						HEMOLYSIN TITRATED; SERUM DOSES					
	0.2	0.1	0.05	0.025	0.0125	0.006	0.2	0.1	0.05	0.025	0.0125	0.006
1	+++	+++	++	—	++	—	+++	+++	++	+++	+	—
2	+++	+++	++	+++	++	—	+++	+++	++	+++	+	—
3	+++	+++	++	+++	+	—	+++	+++	++	+++	—	—
4	+++	+++	++	+++	+	—	+++	+++	++	++	—	—
5	++	++	+	—	—	—	+	+	++	+	—	—
6	+++	+++	++	—	—	—	+++	+++	++	+	—	+
7	+++	+++	++	+++	—	—	+++	+++	++	+++	+	—
8	+++	+++	++	+++	++	—	+++	+++	++	+++	+	—
9	+++	+++	++	+++	+++	+++	+++	+++	++	+++	+++	+++
10	+++	+++	++	+++	+++	+++	+++	+++	++	+++	+++	+++
11	+++	+++	++	+++	+++	+++	+++	+++	++	+++	+++	+
12	+++	+++	++	—	+++	+++	+++	+++	++	+++	+++	—
13	+++	+++	++	+++	+++	—	+++	+++	++	+++	+++	—
14	+++	+++	++	—	—	—	+++	+++	++	+++	+++	—
15	+++	+++	+++	+++	+	—	+++	+++	+++	+	—	—

Similar results with additional sera are shown in Tables VII and VIII under Methods A and B, indicating that with weakly positive and high dilutions of strongly positive sera, the method of using two units of titrated complement generally yields more delicate and sensitive results.

When tests are conducted with sera in amounts of 0.2 or 0.1 c.c. the differences observed with the two methods are not nearly so striking; a resume of such tests is given in Table VI and shows a remarkable similarity of results observed with 236 sera in so far as positive or negative were concerned, 179, or 76 per cent of sera, reacting positive in tests in which the hemolysin was titrated, and 183, or 78 per cent reacting positive in tests in which the complement was titrated. Of the positive reactions, the *latter method gave a higher percentage of strongly positive results*, and the four sera reacting

negative with titrated hemolysin and positive with titrated complement were from luetic individuals undergoing treatment. Similar results are shown in Tables IX and X to which further reference will be made, and the general conclusion at which we arrived is that superior results are observed when the complement is subjected to daily titration rather than the hemolysin, the differences in results being in the nature of more sensitive reactions and a slightly larger percentage of positive reactions with the sera of syphilitic individuals.

TABLE VI

RESULTS OF WASSERMANN TESTS WITH 236 SERA CONDUCTED WITH TITRATED HEMOLYSIN AND CONSTANT AMOUNT OF COMPLEMENT AND TITRATED COMPLEMENT AND CONSTANT AMOUNT OF HEMOLYSIN

METHOD	POSITIVE	NEGATIVE	STRONGLY POSITIVE	WEAKLY POSITIVE
Hemolysin titrated Complement constant	179	57	140	39
Complement titrated Hemolysin constant	183	53	172	11

Part 3

A COMPARATIVE STUDY OF METHODS FOR THE TITRATION COMPLEMENT

The method usually employed consists of titrating complement with one or two units of hemolysin and employing two units in the complement-fixation tests, in order to provide sufficient above and beyond that amount of complement neutralized by the anticomplementary properties of the antigen and serum alone.

Some investigators believing that this amount of complement represents an excess, have modified the technic in order to elicit more delicate reactions; Thomsen⁶ proposed to determine the free unit of complement by titrating in the presence of antigen and using in complement-fixation tests one unit of complement with two units of hemolysin. Boas⁷ also titrates complement in the presence of the extract (antigen) after Thomsen's method, the unit being usually 0.08 c.c. undiluted serum, and uses one unit in the main test with a fixed amount (0.05 c.c.) for the serum control. Later McKenzie⁸ and Browning and McKenzie^{2, 9} proposed an ingenious method for measuring the anticomplementary activity of extract (antigen) and serum alone according to the amount of complement absorbed in units, and subtracting these from the amount absorbed by serum and antigen

together. Still later Loyd Thompson¹⁰ and Thomas and Ivy¹¹ proposed a method combining the principles of Thomsen's and McKenzie's methods consisting in titrating the complement in the presence of antigen and a normal serum to allow for the anticomplementary activities of these substances, and using one unit in the main tests with a unit of hemolysin.

There are, therefore, three methods for the titration of complement as follows:

- (a) Titration of complement with hemolysin alone.
- (b) Titration of complement in the presence of antigen.
- (c) Titration of complement in the presence of antigen and normal serum.

To these may be added the Browning and McKenzie method of adjusting the hemolytic system although not directly concerning the titration of complement alone; *all of these methods have been subjected to comparative tests for the purpose of ascertaining the best for so titrating the complement and adjusting the hemolytic system that complement-fixation tests may be rendered as delicate and sensitive as is possible while avoiding nonspecific reactions.*

Technic.—In order to render the tests strictly comparative, the different methods were studied at the same time with the same complement serum (mixed sera of three or more guinea-pigs), same antigen (cholesterolized heart), same sera (heated), et cetera; in order to elicit differences in sensitiveness the sera were tested in varying amounts. The majority of the tests were conducted with antishoop and antihuman hemolytic systems. The primary and secondary incubations were of one hour in a water bath at 38° C., and the readings were made after the tubes had been placed in a refrigerator over night.

In the tests with results shown in Table VII, the unit of hemolysin as determined by titration with 1 c.c. of 1:20 complement and 1 c.c. of 2.5 per cent suspension of sheep corpuscles was 0.06 c.c. of 1:300; under "Method A" are given the results of tests conducted with 1 c.c. of 1:20 complement and two units of hemolysin. When the complement was titrated with two units of hemolysin the unit was 0.4 c.c. of 1:20 and under "Method B" are shown the results of tests with two units; when the complement was titrated in the presence of antigen the unit was 0.5 c.c. of 1:20 and under "Method C" are given the results observed with one unit and under "Method D" the results ob-

served with two units of complement. Two units of hemolysin were employed in all tests.

In the tests with results shown in Table VIII, the technic was similar; the unit of hemolysin was 0.1 c.c. of 1:300; the unit of complement with two units of hemolysin was 0.3 c.c. of 1:20; the unit of complement titrated in the presence of antigen was 0.4 c.c. of 1:20 and in the presence of antigen and 0.1 c.c. heated normal serum, 0.5 c.c. of 1:20 dilution; all titrations were conducted with two units of hemolysin.

The results shown in Table IX were observed with a similar technic; the unit of hemolysin titrated with 1 c.c. of 1:20 complement and 1 c.c. of 2.5 per cent corpuscles was 0.06 c.c. of 1:300; the unit of complement titrated with antigen and two units of hemolysin was 0.3 c.c. of 1:20 dilution.

The results shown in Table X were observed with a similar technic except that the quantities were altered; the unit of hemolysin titrated with 0.2 c.c. of 1:20 complement and 0.2 c.c. of 2.5 per cent corpuscles was 0.1 c.c. of 1:20,000. The unit of complement titrated in the presence of one unit of hemolysin was 0.15 c.c. of 1:20; titrated in the presence of antigen and one unit of hemolysin the unit was 0.2 c.c. and in the presence of antigen, heated normal serum and one unit of hemolysin, the unit of complement was 0.25 c.c. of 1:20 dilution.

The results shown in Table XI were observed with the antihuman hemolytic system employed by Vedder; the unit of complement was 0.03 c.c. of 1:1½ dilution titrated with one unit of hemolysin and 0.1 c.c. of 5 per cent corpuscles; the unit as titrated in the presence of antigen was 0.05 c.c. and in the presence of antigen and 0.1 c.c. heated normal serum, 0.07 c.c. of 1:1½ dilution.

Results.—In judging the merits of the three methods for adjusting the hemolytic system by titration of the complement, namely, by plain titration, titration in the presence of antigen and titration in the presence of antigen and normal serum, two main criteria were used: (a) whether sufficient complement was furnished to neutralize the anticomplementary activities of antigen and serum and (b) the delicacy and sensitiveness of the reactions as measured by using graded amounts of syphilitic sera.

When complement is titrated in the presence of antigen the unit is usually, but not always, greater than when the complement is

TABLE VII
RESULTS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH COMPLEMENT TITRATED AFTER VARIOUS METHODS

SERA	METHOD A *						METHOD B						METHOD C						METHOD D						
	0.2	0.04	0.008	0.0016	0.0003	0.25 C.	0.2	0.04	0.008	0.0016	0.0003	0.25 C.	0.2	0.04	0.008	0.0016	0.0003	0.25 C.	0.2	0.04	0.008	0.0016	0.0003	0.25 C.	
Syphilitic	3**	1	-	-	-	-	4	1	1	-	-	-	4	3	2	-	-	-	1	3	1	-	-	-	-
Syphilitic	4	2	-	-	-	-	4	3	-	-	-	-	4	4	2	-	-	-	1	4	3	-	-	-	-
Syphilitic	1	1	-	-	-	-	3	2	-	-	-	-	3	3	2	-	-	-	-	4	2	-	-	-	-
Syphilitic	3	2	-	-	-	-	4	4	1	-	-	-	4	4	3	-	-	-	-	3	2	-	-	-	-
Syphilitic	4	3	-	-	-	-	4	1	1	-	-	-	4	4	3	-	-	-	-	3	3	-	-	-	-
Syphilitic	3	1	-	-	-	-	4	3	-	-	-	-	4	4	3	-	-	-	-	3	3	-	-	-	-
Syphilitic	3	3	-	-	-	-	3	3	-	-	-	-	4	4	4	-	-	-	-	3	4	-	-	-	-
Syphilitic	4	4	-	-	-	-	4	4	1	-	-	-	4	4	4	-	-	-	-	1	4	-	-	-	-
Syphilitic	2	1	-	-	-	-	3	2	-	-	-	-	4	4	3	-	-	-	-	4	4	-	-	-	-
Syphilitic	4	4	-	-	-	-	4	4	-	-	-	-	4	4	4	-	-	-	-	4	4	-	-	-	-
Syphilitic	3	3	-	-	-	-	4	4	-	-	-	-	4	4	4	-	-	-	-	3	4	-	-	-	-

* Method A.—Complement used in fixed amount of 1 c.c. of 1:20; hemolysin titrated and used in two units.

Method B.—Complement titrated with two units hemolysin; tests conducted with two units of complement and two units of hemolysin.

Method C.—Complement titrated with antigen and two units of hemolysin; tests conducted with one u. of complement and two units of hemolysin.

Method D.—Same as C except that tests were conducted with two units of complement and two units of hemolysin.

** 4 = ++++; 3 = +++ etc.

TABLE VIII
RESULTS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH AN ANTISHEEP HEMOLYTIC SYSTEM,
COMPLEMENT BEING TITRATED WITH DIFFERENT METHODS.

SERA	METHOD A*				METHOD B				METHOD C				METHOD D				METHOD E				METHOD F			
	0.15	0.02	0.002	0.15 S. C.	0.15	0.02	0.002	0.15 S. C.	0.15	0.02	0.002	0.15 S. C.	0.15	0.02	0.002	0.15 S. C.	0.15	0.02	0.002	0.15 S. C.	0.15	0.02	0.002	0.15 S. C.
Syphilitic	4**	1	-	-	4	4	-	-	4	4	-	-	4	4	3	-	4	4	-	-	4	1	-	-
Syphilitic	4	1	-	-	4	4	-	-	4	4	-	-	4	4	4	-	4	4	-	-	4	1	-	-
Syphilitic	3	-	-	-	3	1	-	-	1	1	-	-	3	1	1	-	2	2	-	-	3	-	-	-
Syphilitic	3	-	-	-	3	1	-	-	1	1	-	-	4	4	1	-	4	4	-	-	3	-	-	-
Syphilitic	1	-	-	-	4	4	-	-	4	4	-	-	4	4	4	-	4	4	-	-	4	-	-	-
Syphilitic	4	1	-	-	4	3	-	-	4	4	-	-	4	4	1	-	4	4	-	-	3	-	-	-
Syphilitic	4	-	-	-	4	4	-	-	4	4	-	-	4	4	4	-	4	4	-	-	4	-	-	-
Syphilitic	3	-	-	-	4	4	-	-	4	4	-	-	4	4	4	-	4	4	-	-	4	-	-	-
Syphilitic	1	-	-	-	2	1	-	-	2	2	-	-	1	1	1	-	1	1	-	-	2	-	-	-
Syphilitic	1	-	-	-	4	4	-	-	4	4	-	-	4	4	4	-	4	4	-	-	2	-	-	-
Syphilitic	2	-	-	-	4	4	-	-	4	4	-	-	4	4	3	-	4	4	-	-	2	-	-	-
Syphilitic	1	1	-	-	4	4	-	-	1	1	-	-	4	4	2	-	4	4	-	-	3	-	-	-
Syphilitic	3	-	-	-	4	3	-	-	4	4	-	-	4	4	3	-	4	4	-	-	2	-	-	-
Syphilitic	1	-	-	-	4	2	-	-	4	4	-	-	4	4	2	-	4	4	-	-	1	-	-	-
Syphilitic	4	2	-	-	4	4	-	-	4	4	-	-	4	4	2	-	4	4	-	-	4	-	-	-
Syphilitic	4	1	-	-	4	4	-	-	4	4	-	-	4	4	4	-	4	4	-	-	4	-	-	-
Syphilitic	4	3	-	-	4	4	-	-	4	4	-	-	4	4	4	-	4	4	-	-	4	-	-	-
Syphilitic	4	4	-	-	4	4	-	-	4	4	-	-	4	4	4	-	4	4	-	-	4	-	-	-
Syphilitic	4	4	-	-	4	4	-	-	4	4	-	-	4	4	4	-	4	4	-	-	4	-	-	-
Syphilitic	4	1	-	-	4	4	-	-	4	4	-	-	4	4	3	-	4	4	-	-	4	-	-	-
Normal	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Normal	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Normal	-	-	-	-	1	-	-	-	1	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-

*Method A.—Complement used in fixed amount of 1 c.c. of 1:20 dilution; hemolysin titrated and used in 2 units.
 Method B.—Complement titrated with 2 units of hemolysin and 2 units employed with 2 units of hemolysin.
 Method C.—Complement titrated in presence of antigen and 1 unit used with 2 units of hemolysin.
 Method D.—Same as C except 2 units of complement used.
 Method E.—Complement titrated in presence of antigen and normal serum and 1 unit used with 2 units of hemolysin.
 Method F.—Same as E except 2 units of complement used.
 **4 = +++++; 3 = ++++; 2 = ++; 1 = +; — = negative.

TABLE IX
COMPARATIVE COMPLEMENT-FIXATION TESTS USING COMPLEMENT IN FIXED DOSE AND
COMPLEMENT TITRATED IN THE PRESENCE OF ANTIGEN

SERA	METHOD A *										METHOD B										METHOD C										METHOD D																
	0.2	0.1	0.05	0.025	0.0125	0.006	0.003	0.0015	0.0008	0.2 S. C.	0.2	0.1	0.05	0.025	0.0125	0.006	0.003	0.0015	0.0008	0.2 S. C.	0.2	0.1	0.05	0.025	0.0125	0.006	0.003	0.0015	0.0008	0.2 S. C.	0.2	0.1	0.05	0.025	0.0125	0.006	0.003	0.0015	0.0008	0.2 S. C.							
Syphilitic	4**	4	4	4	4	4	3	1	—	—	4	4	4	4	4	4	3	2	—	—	4	4	4	4	4	4	4	3	2	1	—	—	4	4	4	4	4	4	4	4	0.0008	0.0015	0.0008	0.2 S. C.			
Syphilitic	4	4	4	4	4	4	3	1	—	—	3	4	4	4	4	4	3	1	1	—	—	3	4	4	4	4	4	3	2	1	—	—	4	4	4	4	4	4	4	4	4	4	0.0008	0.0015	0.0008	0.2 S. C.	
Syphilitic	4	4	4	4	4	4	3	2	—	—	—	4	4	4	4	4	4	3	1	—	—	—	4	4	4	4	4	4	3	2	1	—	—	4	4	4	4	4	4	4	4	4	4	0.0008	0.0015	0.0008	0.2 S. C.
Syphilitic	4	4	4	4	4	4	3	—	—	—	—	4	4	4	4	4	4	2	—	—	—	4	4	4	4	4	4	4	2	—	—	—	—	4	4	4	4	4	4	4	4	4	4	0.0008	0.0015	0.0008	0.2 S. C.

*Method A.—Complement in fixed dose of 1 c.c. of 1:20; hemolysin titrated and used in 2 units.

Method B.—Complement titrated in presence of cholesterolized antigen and used in 1 unit with 1 unit of hemolysin.

Method C.—Same as B except that 2 units of complement were employed.

Method D.—Same as C except that 2 units of hemolysin were employed.

**4 = ++++; 3 = +++; 2 = ++; 1 = +; — = negative.

TABLE X
RESULTS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH AN ANTISHEEP HEMOLYTIC SYSTEM,
COMPLEMENT BEING TITRATED WITH DIFFERENT METHODS

	METHOD A*				METHOD B				METHOD C				METHOD D				METHOD E				METHOD F				METHOD G						
	0.1	0.025	0.00625	0.0015	0.004	0.1 S. C.	0.1	0.025	0.00625	0.0015	0.004	0.1 S. C.	0.1	0.025	0.00625	0.0015	0.004	0.1 S. C.	0.1	0.025	0.00625	0.0015	0.004	0.1 S. C.	0.1	0.025	0.00625	0.0015	0.004	0.1 S. C.	
Syphilitic	4**	4	4	4	4	3	1	1	1	1	1	1	4	4	2	1	1	1	1	4	4	2	3	1	1	4	4	1	1	1	
Syphilitic	4	3	1	1	1	1	4	3	1	1	1	1	3	1	1	1	1	1	1	4	3	1	1	1	1	4	3	2	1	1	
Syphilitic	4	4	4	4	4	1	1	1	1	1	1	1	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
Syphilitic	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
Syphilitic	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
Syphilitic	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
Syphilitic	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
Syphilitic	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
Normal	4	4	4	4	4	3	1	1	1	1	1	1	4	4	2	1	1	1	1	4	4	1	3	1	1	4	4	1	1	1	1
Normal	4	4	4	4	4	3	1	1	1	1	1	1	4	4	2	1	1	1	1	4	4	1	3	1	1	4	4	1	1	1	1

*Method A.—Complement used in constant dose of 0.2 of 1:20; hemolysin titrated and used in 2 units.

Method B.—Complement titrated with 1 unit of hemolysin and 2 units used with 1 unit of hemolysin.

Method C.—Same as B except that 2 units of complement and 2 units of hemolysin used.

Method D.—Complement titrated in presence of antigen and 1 unit of hemolysin; 2 units of complement and 1 unit of hemolysin employed.

Method E.—Same as D except that 2 units of complement and 2 units of hemolysin were used.

Method F.—Complement titrated in presence of antigen, 0.1 c.c. heated normal serum and 1 unit of hemolysin; tests were conducted with 1 unit of complement and 1 unit of hemolysin.

Method G.—Same as F except that tests were conducted with 2 units of complement and 1 unit of hemolysin.

** 4 = +++++; 3 = ++++; 2 = ++; 1 = +; — = negative.

TABLE XI
RESULTS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH AN ANTHUMAN HEMOLYTIC SYSTEM,
COMPLEMENT BEING TITRATED WITH DIFFERENT METHODS

[illegible]

Method A.—Complement titrated with 1 unit of hemolysin and 2 units used with 2 units of hemolysin.
Method B.—Complement titrated in the presence of antigen with 1 unit of hemolysin and 1 unit used with 2 units of hemolysin.
Method C.—Same as B except that 2 units of complement were employed.
Method D.—Complement titrated in the presence of antigen 0.1 c.c. heated normal serum and 1 unit of hemolysin in 1 unit used with 2 units of hemolysin.
Method E.—Same as D except that 2 units of complement were used.

titrated alone; this depends upon the nature of the antigen (cholesterolized extracts absorb more complement than plain extracts) and the amount employed. When complement is titrated in the presence of antigen and normal heated serum, the unit is usually, but not always, higher than the unit observed in the plain titration and in the presence of antigen; this depends upon the amount of natural hemolysin present in the serum and whether or not the serum has acquired thermostabile anticomplementary activity, in which case the unit is always higher. In Table XII are summarized the units of complement observed in various experiments; the presence of antigen usually increased the unit and the presence of serum still more so, and particularly in the antihuman system, owing to the absence of natural hemolysin.

TABLE XII

THE INFLUENCE OF ANTIGEN AND OF ANTIGEN AND NORMAL HEATED
SERUM UPON COMPLEMENT TITRATIONS

HEMOLYTIC SYSTEM	DILUTION OF COMPLEMENT	UNIT OF COMPLEMENT		
		Plain Titration c.c.	In presence of antigen c.c.	In presence of antigen and serum. c.c.
Antisheep	1:20	0.15	0.2	0.3
Antisheep	1:20	0.3	0.4	0.5
Antisheep	1:20	0.2	0.2	0.25
Antisheep	1:20	0.3	0.4	0.4
Antisheep	1:20	0.4	0.6	0.7
Antihuman	1:1½	0.03	0.05	0.05
Antihuman	1:1½	0.02	0.03	0.05
Antihuman	1:1½	0.03	0.05	0.07
Antihuman	1:1½	0.03	0.05	0.08
Antihuman	1:10	0.08	0.12	0.2

The general results may be summarized as follows, the details and actual differences being best shown in the tables; owing to the differences observed with the two hemolytic systems it is necessary to summarize the results separately.

Results with Antisheep Hemolytic Systems.—1. The general practice is to use two units of complement, titrated plain (that is, in the absence of antigen and serum) with two units of hemolysin; *better results were observed with two units of complement titrated in the presence of antigen and one unit of hemolysin.*

2. Tests conducted with two units of complement titrated plain and one unit of hemolysin, yielded too many anticomplementary reactions;

likewise tests conducted with one unit of complement and two units of hemolysin.

3. Tests conducted with two units of complement titrated in the presence of antigen and two units of hemolysin were much less sensitive than tests conducted with two units of complement titrated plain and two units of hemolysin; also less sensitive than tests conducted with two units of complement titrated in the presence of antigen and one unit of hemolysin.

4. Tests conducted with one unit of complement titrated in the presence of antigen and heated normal serum and one unit of hemolysin yielded very sensitive reactions, but with frequent incomplete hemolysis of the serum controls due to too close adjustment of the hemolytic system; this system was generally somewhat more sensitive than tests conducted with two units of complement titrated in the presence of antigen and one unit of hemolysin and distinctly more so than tests conducted with two units of complement titrated plain and two units of hemolysin.

5. Tests conducted with two units of complement titrated in the presence of antigen and normal serum and one unit of hemolysin, were distinctly less sensitive owing to an excess of complement under these conditions.

Results with an Antihuman Hemolytic System.—1. The general practice is to conduct tests with two units of complement titrated plain and two units of hemolysin; tests conducted with one unit of complement titrated in the presence of antigen and two units of hemolysin, were much more sensitive, but yielded a high percentage of anticomplementary reactions due to too close adjustment of the hemolytic system.

2. Tests conducted with two units of complement titrated in the presence of antigen and two units of hemolysin yielded reactions almost identical with those conducted with two units of complement titrated plain and two units of hemolysin; slight differences were in favor of the method of titrating complement in the presence of antigen and generally consisted of sharper hemolysis and fewer instances of incomplete hemolysis of the serum controls, because the unit of complement was generally somewhat greater.

3. Tests conducted with one unit of complement titrated in the presence of antigen and heated normal serum and one unit of hemolysin yielded a very high percentage of anticomplementary results

and are not shown in Table XI; similar tests with two units of hemolysin yielded very sensitive results, but several anticomplementary reactions, and were somewhat inferior to tests conducted with two units of complement titrated plain and two units of hemolysin. Tests conducted with two units of complement titrated with antigen and serum and two units of hemolysin were distinctly less sensitive than reactions with the other methods due to excess of complement under these conditions.

Plain Titration of Complement.—The results therefore, bear a direct relation to the amount of complement furnished in the hemolytic system; generally this amount may be smaller and more closely adjusted in an antsheep than an antihuman system because of the presence of natural antsheep hemolysin in the majority of sera and the use of more powerful immune hemolysin. Experience has shown that with both systems it is necessary to use two units of complement titrated plain (that is, without antigen and normal serum) and two units of hemolysin in order to obtain satisfactory results in practical work with sera of varying degrees of freshness and anticomplementary activity.

Titration of Complement in Presence of Antigen.—A closer adjustment for the antsheep system consists in titrating the complement in the presence of antigen and one unit of hemolysin after Thomsen's method and using two units with one unit of hemolysin in the complement-fixation tests; with the antihuman system two units of complement and two units of hemolysin must be used. This method has yielded us particularly good results and is worthy of serious consideration as the method of choice for adjusting the hemolytic system.

Titration of Complement in the Presence of Antigen and Normal Serum.—This ingenious method devised by Thompson¹⁰ and also advocated by Thomas and Ivy,¹¹ would appear to be satisfactory and is based upon good principles, but in actual practice it has two distinct drawbacks when used with an antsheep system as is the practice of Thomas and Ivy, namely, (1) the single or pooled normal serum for the titrations may carry over considerable natural antsheep hemolysin and thereby yield a unit of complement too small for the testing of sera containing none or smaller amounts of natural hemolysin. Ottenberg¹² has already drawn attention to this objection and we believe it is a factor of importance when the titrations are made with

due care and the unit exactly read instead of with laxity, that is, taking one or two doses higher than the smallest amount of complement giving complete hemolysis; the objection does not hold, however, with Thompson's technic because an antihuman system is employed. Most of our sera were tested within three days of collection and were free of anticomplementary activity, but with this method the serum controls frequently showed a slight deposit of cells next day sufficient to disturb accurate readings. (2) Titration of complement in the presence of pooled sera was greatly influenced by the age of the serum or sera employed; if sera more than five days old were used the unit was invariably higher by one or two tubes than when fresh serum was employed because of thermostabile anticomplementary properties. The unit therefore would be unnecessarily high for tests with perfectly fresh sera. Titrations with fresh sera free of anticomplementary activities frequently yielded a unit just a trifle too small for testing sera somewhat older, that is, the serum controls would not show complete sparkling hemolysis which is so desirable in complement-fixation tests.

This technic was considered so important, however, that more extensive studies were made by subjecting a large series of syphilitic sera to comparative tests; each serum was tested with three different antigens in a method employing 1 c.c. of complement 1:20 as a constant dose with two units of hemolysin titrated with each complement serum and after the method of Thomas and Ivy. In order to render the tests strictly comparative, the latter tests were conducted with the same alcoholic extract of syphilitic liver as used in the former tests; likewise the complement was made up of the pooled sera of the same guinea pigs and the primary and secondary incubations of the same duration in a water-bath at 38° C. All readings were made after the tubes had stood in a refrigerator over night.

Table XIII shows the results observed with twenty sera; \pm in the table means the presence of corpuscles (less than 25 per cent of the whole) frequently found in the serum controls and disturbing the readings. Table XIV gives a summary of results with 240 sera in which accurate readings could be made; the great majority of these sera other than those taken from healthy individuals for known negative controls, were from persons undergoing treatment for syphilis in the clinic of Dr. Schamberg. As shown in Table XIV the routine test yielded 95.8 per cent positive reactions and in so far as it was

possible to ascertain, all were true reactions; the Thomas-Ivy method yielded 90 per cent positive reactions, that is, missed about 6 per cent reactions with syphilitic sera.

TABLE XIII

COMPARATIVE COMPLEMENT-FIXATION TESTS WITH THE WASSERMANN
AND THOMAS-IVY METHODS

HISTORY	REGULAR WASSERMANN TESTS; 3 ANTIGENS*				THOMAS AND IVY TESTS	
	C.B.H.	Plain	A	Serum Controls	Plain Antigen	Serum Controls
Healthy individual	—**	—	—	—	+++	++
Secondary syphilis	++++	++++	++++	—	++++	—
Healthy individual	—	—	—	—	+	±
Healthy individual	—	—	—	—	—	—
Syph. under treatment	+++	+++	+++	—	++++	±
Syph. under treatment	++++	++++	++++	—	++++	±
Syph. under treatment	++++	++++	++++	—	++++	±
Syph. under treatment	++++	++++	++++	—	++++	±
Syph. under treatment	++++	++++	++++	—	++++	—
Syph. under treatment	++++	++++	++++	—	++++	—
Syph. under treatment	+	+	+	—	+	—
Syph. under treatment	—	—	—	—	—	—
Syph. under treatment	++++	++++	++++	—	+++	—
Syph. under treatment	++++	++++	++++	—	+	—
Syph. under treatment	++++	++++	++++	—	++++	±
Syph. under treatment	++++	++++	++++	—	++++	±
Syph. under treatment	++++	++++	++++	—	++++	—
Syph. under treatment	++++	++++	++++	—	++++	—
Syph. under treatment	—	—	—	—	—	—
Syph. under treatment	—	—	—	—	+	±

* C.B.H. = cholesterolized beef heart; Plain = alcoholic extract syphilitic liver; A = acetone insoluble lipoids.

** +++++ = absolute inhibition of hemolysis; +++ = 75 per cent inhibition; ++ = 50 per cent inhibition; + = 25 per cent inhibition; ± = less than 25 per cent inhibition of hemolysin.

TABLE XIV

COMPARATIVE RESULTS OF WASSERMANN TESTS WITH SERA FROM 240 SYPHILITIC
PERSONS CONDUCTED WITH A CONSTANT AMOUNT OF COMPLEMENT AND
TWO UNITS OF HEMOLYSIN AND WITH ONE UNIT OF COMPLEMENT
TITRATED IN THE PRESENCE OF ANTIGEN AND NORMAL
SERUM AND ONE UNIT OF HEMOLYSIN*

METHOD	POSITIVE	NEGATIVE	PERCENTAGE POSITIVE REACTIONS
Complement constant; hemolysin titrated**	230	10	95.8
Complement titrated in presence of antigen and serum; hemolysin constant†	216	24	90

* All tests conducted with the same alcoholic extract of syphilitic liver.

** Complement 1 c.c. of 1:20; 2 units of hemolysin used.

† Technic of Thomas and Ivy.

Method of Browning and McKenzie.—Mention has already been made of this technic which measures the anticomplementary activity of each serum and the antigen separately according to the units of complement absorbed or fixed and subtracting these from the units

TABLE XV
RESULTS OF COMPLEMENT-FIXATION TESTS WITH A MODIFICATION OF THE BROWNING-McKENZIE METHOD

HISTORY	WASSERMANN TESTS			QUANTITATIVE COMPLEMENT-FIXATION TESTS						SERUM CONTROLS		AMOUNT OF COMPLEMENT ABSORBED
	C.H.	S	A	2 Units	3 Units	4 Units	5 Units	6 Units	8 Units	1 Unit	2 Units	
Latent Syphilis	+++*	+++	+++	++++	++++	++++	+++	+++	+++	+	+	5 units
Secondary Syphilis	+++	+++	+++	++++	++++	++++	+++	+++	+++	+	+	8 units
Primary Syphilis	+++	+++	+++	++++	++++	++++	+++	+++	+++	+	+	5 units
Chronic Gonorrhea	+++	+++	+++	++++	++++	++++	+++	+++	+++	+	+	none
Latent Syphilis	+++	+++	+++	++++	++++	++++	+++	+++	+++	+	+	3 units
Secondary Syphilis	+++	+++	+++	++++	++++	++++	+++	+++	+++	+	+	8 units
Tertiary Syphilis	+++	+++	+++	++++	++++	++++	+++	+++	+++	+	+	5 units
Secondary Syphilis	+++	+++	+++	++++	++++	++++	+++	+++	+++	+	+	8 units
Cured Syphilis	+++	+++	+++	++++	++++	++++	+++	+++	+++	+	+	none
Gonorrhea	+++	+++	+++	++++	++++	++++	+++	+++	+++	+	+	none
Chancroid	+++	+++	+++	++++	++++	++++	+++	+++	+++	+	+	none
Gonorrhea	+++	+++	+++	++++	++++	++++	+++	+++	+++	+	+	none

* ++++ = strongly positive (absolute inhibition of hemolysis); +++ = moderately positive (75 per cent inhibition of hemolysis); ++ = weakly positive (50 per cent inhibition of hemolysis); + = very weakly positive (25 per cent inhibition of hemolysis); -- = negative.

fixed by mixtures of serum and antigen as a measure of the degree of complement fixation. We have used a modification of this technic¹³ with excellent results; the chief objections are the large amounts of complement required and the labor and time involved.

In our technic an antishoop hemolytic system was used instead of an antiox and the complement was titrated in the presence of antigen, thereby removing the necessity of testing the anticomplementary activity of the antigen each time tests are made after the method of Browning and McKenzie. Furthermore, we did not sensitize the corpuscles and used but one unit of hemolysin; complement was used in two, three, four, five, six and eight units instead of the very large amounts advocated by Browning and McKenzie and the readings were different, that is, a reaction was regarded as positive when lysis was incomplete with two units of complement, in addition to the amount absorbed by the serum alone.

The results were excellent and the readings usually sharp and easily read; with further improvements the method could bid for acceptance as a standardized method except for the expense of large amounts of complement serum and greatly increased labor involved. The results of a few tests conducted with a cholesterolized extract are shown in Table XV with the results of the routine modified Wassermann test for comparison; a summary of comparative tests with sixty sera is given in Table 16. These sera were carefully chosen and furnished by Dr. William MacKinney and the results of the complement-fixation tests generally agreed with the clinical expectancy of each case. As shown in Table XVI, the sera of three persons reacted negatively in the modified Browning and McKenzie tests, and positively in the modified Wassermann; two of these sera were from cases in whom Dr. MacKinney expected negative reactions (case chronic prostatitis; case of impotence) and the third was from a case of latent syphilis, in whom a positive reaction was expected.

TABLE XVI

SUMMARY OF TESTS CONDUCTED WITH THE WASSERMANN AND MODIFIED
BROWNING-MCKENZIE METHODS

METHOD	POSITIVE	NEGATIVE
Modified Wassermann tests; hemolysin titrated	21	39
Modified Browning and McKenzie tests; complement titrated	18	42

Part 4

TECHNICAL FACTORS IN THE TITRATION OF COMPLEMENT

In the titration of complement, air (thermostat) or water-bath incubation are commonly employed, the time allowed for hemolysis by different serologists varying from one-half to two hours. As a general rule one-half hour in a water-bath is believed equivalent to one hour in an air incubator, hemolysis being more rapid in the former because the mixtures in test tubes are warmed more quickly.

The results of an experiment given in Table XVII were observed with the titration of complement diluted 1:20 with one unit of anti-sheep hemolysin and 0.2 c.c. of 2.5 per cent suspension of sheep corpuscles; the results observed in a second experiment in which comple-

TABLE XVII

THE COMPARATIVE SPEED OF HEMOLYTIC ACTIVITY OF COMPLEMENT
TITRATED IN A WATER-BATH AND IN AN AIR THERMOSTAT

TIME	Unit of Complement 1:20	
	Air incubation	Water-bath
15 min.	more than 2 c.c.	more than 2 c.c.
30 min.	more than 2 c.c.	more than 2 c.c.
60 min.	more than 2 c.c.	2 c.c.
1½ hours	2 c.c.	1 c.c.
2 hours	1.5 c.c.	1 c.c.
2½ hours	1 c.c.	1 c.c.
3 hours	1 c.c.	1 c.c.
3½ hours	0.9 c.c.	0.7 c.c.
4 hours	0.7 c.c.	0.7 c.c.
4 hours*	0.5 c.c.	0.5 c.c.

* Then placed in a refrigerator for 20 hours.

ment diluted 1:20 was titrated with two units of antisheep hemolysin and 1 c.c. of 2.5 per cent suspension of sheep corpuscles, are shown in Table XVIII. In both experiments *water-bath incubation hastened hemolysis*, one hour being about equivalent in effect to one and a half hours in air incubation.

At least one hour incubation in a water-bath is required for the titration of complement and one and a half to two hours if the incubation is conducted in a thermostat; the units of hemolytic activity usually remain unchanged after these periods until incubation is prolonged to three and a half and four hours when a slight increase of hemolysis takes place, the maximum of hemolytic activity of complement being observed after the tubes have been placed in a refrigerator over night.

TABLE XVIII

THE COMPARATIVE SPEED OF HEMOLYTIC ACTIVITY OF COMPLEMENT
TITRATED IN A WATER-BATH AND IN AIR THERMOSTAT

TIME	Unit of Complement 1:20	
	Air incubation	Water-bath
15 min.	0.6 c.c.	0.2 c.c.
30 min.	0.25 c.c.	0.15 c.c.
60 min.	0.15 c.c.	0.1 c.c.
1½ hours	0.1 c.c.	0.1 c.c.
2 hours	0.1 c.c.	0.1 c.c.
2½ hours	0.1 c.c.	0.1 c.c.
3 hours	0.1 c.c.	0.1 c.c.
3½ hours	0.1 c.c.	0.09 c.c.
4 hours	0.1 c.c.	0.08 c.c.
4 hours*	0.1 c.c.	0.08 c.c.

* Then placed in refrigerator for 20 hours.

When complement is titrated in the presence of antigen after the method of Thomsen, and in the presence of antigen and normal serum after the method of Thompson and Thomas and Ivy, the mixtures should be incubated at least one hour before the addition of hemolysin and corpuscles to elicit the full degree of nonspecific fixation by antigen or antigen and serum. As shown in Table XIX slightly more complement is fixed or absorbed by antigen alone or by antigen and normal serum after one hour incubation in a water-bath than after one half hour. As shown in Table XX at least one hour more must be allowed after the addition of hemolysin and corpuscles before the unit of complement may be read with water-bath

TABLE XIX

THE INFLUENCE OF THE DURATION OF PRIMARY INCUBATION IN A WATER-BATH
UPON THE HEMOLYTIC ACTIVITY OF COMPLEMENT TITRATED BY
VARIOUS METHODS

METHOD OF TITRATING COMPLEMENT	UNITS OF COMPLEMENT WITH DIFFERENT ANTIGENS*			
	Cholest.	Plain alc. beef heart	Plain alc. syph. liver	Acet. insol. lipoids.
Plain titration (no antigen; no serum)**	0	0	0	0
Complement and antigen in- cubated ½ hour†	0.25	0.5	0.7	0.6
Complement and antigen in- cubated 1 hour†	0.3	0.6	0.4	0.5
Complement, antigen and serum incubated ½ hour†	0.2	0.2	0.25	0.2
Complement, antigen and serum incubated 1 hour†	0.25	0.25	0.25	0.25

* At the end of 1 hour of incubation in a water-bath at 38° C.

** 0.25 c.c.

† Before the addition of 1 unit of hemolysin and corpuscles.

incubation; at this time the unit is acceptable as a practical measure of hemolytic activity although the unit of maximum activity is not determined until incubation is continued for four hours or longer as stated above.

TABLE XX
THE SPEED OF HEMOLYTIC ACTIVITY OF COMPLEMENT TITRATED BY
DIFFERENT METHODS

TIME*	UNITS OF COMPLEMENT DILUTED 1:20				
	Plain titration	Complement and antigen ½ hour**	Complement and antigen 1 hour	Complement, antigen and serum ½ hour	Complement, antigen and serum 1 hour
	more than	more than	more than		
15 min.	0.5	0.5	0.5	0.25	0.3
30 min.	0.3	0.4	0.4	0.2	0.25
60 min.	0.25	0.25	0.3	0.2	0.25
1½ hrs.	0.2	0.2	0.3	0.2	0.2
2 hrs.	0.2	0.2	0.25	0.2	0.2
2½ hrs.	0.2	0.2	0.25	0.2	0.2
3 hrs.	0.15	0.15	0.25	0.15	0.2

* In a water-bath at 33° C.

** With a cholesterolized extract.

It will be noted in Tables XVIII and XIX that when complement is titrated in the presence of 0.1 c.c. fresh heated normal serum, the unit is frequently smaller than when titrated in the presence of antigen alone; this is apparently due to the presence of natural anti-sheep hemolysin in the human serum. As previously stated, the unit may, however, be higher when complement is titrated in the presence of serum if the latter contains thermostable anticomplementary substances which serve to absorb or fix larger amounts of complement. Because of these two variations introduced into the titration when normal human serum is used, we believe that it is better practice to omit normal human serum in the titration of complement.

Experiments upon the possible influence of the manner of mixing the ingredients upon the results of complement titrations have not disclosed any facts of practical importance except that when complement, corpuscles, and hemolysin are mixed at once as in the plain or usual method of titrating complement, it is well not to mix the corpuscles and hemolysin for five minutes or more before adding complement, because this exposure results in sufficient sensitization of the cells to appreciably enhance the degree of hemolytic activity of the complement.

Part 5**PRINCIPLES OF A STANDARDIZED METHOD FOR THE TITRATION OF
COMPLEMENT**

In a previous article¹ due emphasis has been placed upon the necessity of using the mixed sera of several guinea pigs for complement in order to equalize differences in hemolytic activity and fixability; also the influence of certain factors in the collection and preparation of the complement serum. In the titration of complement for complement-fixation tests we believe the following principles of primary importance:

1. To so adjust the amounts of corpuscles and hemolysin that the unit of complement will fall within a range neither too large nor too small for the most sensitive and specific complement-fixation reactions, this range must be decided upon by actual experience with any given technic and may require the daily titration of hemolysin preliminary to the titration of complement in order to avoid using too much or too little hemolysin.

2. Complement should be titrated in the presence of the test dose of antigen in order to allow for the nonspecific fixation or absorption of complement by this ingredient.

3. In titrating complement, the mixtures of complement and antigen should be placed in a water-bath at 38° C. for at least one hour before the addition of hemolysin and corpuscles.

4. After the addition of hemolysin and corpuscles a secondary incubation of one hour is advisable before reading the unit of complement, although experience may show that a safe reading may be made at the end of half an hour.

5. For the syphilis complement-fixation test it is not necessary to make a preliminary titration of the fixability of complement *provided the mixed sera of at least three or more guinea pigs are employed*; as shown in a previous article¹³ complement serum may be preserved for at least two weeks in order to avoid waste and this is to be preferred to the use of the serum of a single animal.

The technical details of a method for the titration of complement for a standardized complement-fixation test embodying these principles will be given in a later communication.

CONCLUSIONS

1. The hemolytic system for complement-fixation tests should be so adjusted that the amount of complement employed is neither unnecessarily large, which tends to falsely negative complement-fixation reactions in the presence of small amounts of syphilis antibody, nor too small, which does not allow for complement absorption by serum and extract alone and for complement destruction during the period of primary incubation.

2. The use of excessive amounts of hemolysin in the titration of complement may reduce the amount of the latter so greatly that the unit will not allow sufficient for the nonspecific factors operative in all complement-fixation tests.

3. *Adjustment of the hemolytic system by daily titrations of complement has proved superior to adjustment by daily titrations of hemolysin for the conduct of complement-fixation tests for syphilis.*

4. For practical purposes in routine complement-fixation tests when the complement is titrated plain (that is, in the absence of antigen and normal serum) it is necessary to use at least two units of complement and two units of hemolysin to allow for nonspecific absorption by serum and extract alone and for deterioration of complement during incubation.

5. *With an antisheep hemolytic system best results were observed by titrating complement in the presence of antigen and using two units with one unit of hemolysin.* With an antihuman system this method renders the adjustment too close and requires the use of two units of complement and two units of hemolysin.

6. Titration of complement in the presence of extract and pooled nonsyphilitic serum and the use of exactly one unit so obtained with one unit of hemolysin, was found a good method but open to error due to varying amounts of natural antisheep hemolysin and anti-complementary substances in the pooled serum used in the titration, which so influenced the titrations as to yield a unit of complement too large for some sera and too small for others.

7. A modified method for measuring the amount of complement absorbed by extract and serum alone yielded excellent results, but is not suitable for routine work because of the large amounts of complement serum required and labor involved.

8. In the titration of complement the unit of hemolytic activity is more quickly obtained by water bath incubation than by air (thermo-

stat) incubation, one hour in the former being equal to one and a half to two hours in the latter.

9. When complement is titrated in the presence of antigen or of antigen and normal serum, the mixtures should be incubated in a water-bath for at least one hour before the addition of corpuscles and hemolysin in order to elicit the full degree of nonspecific fixation or absorption of complement by these substances.

10. The principles of a standardized method for the titration of complement based upon the results of these studies, are given in this communication.

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A NOTE ON SYPHILITIC (?) PARENCHYMATOUS NEPHRITIS

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COLE'S recent report of a case of acute syphilitic nephritis leads me to present the following observations on a case of parenchymatous nephritis at first believed to be of syphilitic origin, which responded temporarily to arsphenamine therapy with subsequent complete and permanent relapse. This case illustrates some of the difficulties which the diagnosis of this apparently rather rare condition may present.

CASE REPORT

Case 250104. A Bulgarian, aged thirty-three, came to the clinic complaining of "syphilis, pain like kill" in the abdomen. It was impossible at the time to find an interpreter who understood the patient's dialect so that his history lacks detail. He complained further of nocturnal aching pains in the calves, weakness, and sore mouth and throat. Eighteen months before he had had a penile lesion of one month's duration, followed by a sore mouth at intervals for a year. Three months before he came to the clinic, pain in the abdomen had developed with the nocturnal myalgia. A tonsillectomy had been done at this time. While it was impossible to get a clear history of antiluetic treatment, the patient had evidently received some medicine, not intramuscular or intravenous, from the physician who told him he had syphilis.

Objective examination disclosed the following findings:

Patient pale, but fairly nourished.

Scar of healed lesion on the frenum of the penis.

Pharynx markedly engorged and reddened.

Marked general adenopathy, involving inguinal, epitrochlear and posterior cervical groups.

Moderate pyorrhea, and several carious but not devitalized teeth.

Tonsils cleanly removed.

No nasal focus of infection.

A few coarse rales at both lung bases.

Diffuse abdominal tenderness with slight rigidity.

No ascites, or edema of face or extremities.

Fundus oculi, low grade neuroretinitis.

Blood pressure 104/80.

Serum Wassermann reaction negative.

Hemoglobin 80 per cent, leucocytes 12,600.

Blood urea 10 mg. per 100 c.c.

Phenolsulphonaphthalein test 30 per cent (subcutaneous).

The urinalysis showed a range in specific gravity from 1012 to 1022. The quantity of albumin averaged about one-half volume; there were many waxy and hyaline casts and a few of the granular type, with occasional red blood cells. On two separate occasions there was no difficulty in demonstrating that many of the granular and waxy casts were made up of globules of double-refracting lipoids. (Fig. 1.) Two catheterized specimens were searched for *Spirocheta pallida* with negative results.

The history of infection with penile scar, pharyngitis, general adenopathy, and low-grade neuroretinitis, with double-refractive lipoids and a tremendous albuminuria seemed to justify a therapeutic test with arsphenamine, in spite of the negative Wassermann test, which might be explained by treatment. Such a test was thereupon inaugurated, with very interesting results (Fig. 2). During the twenty-four hours following the administration of 1 dg. of arsphenamine, the albumin and cast content of the urine rose to three-fourths as much again by volume as in previous examinations and then subsided almost to zero, suggesting a Herxheimer effect. The improvement was of short duration, and the injection was repeated in five days, using 3 dg. Again the Herxheimer-like curve in the albumin content appeared, much more marked than with 1 dg., but relapse was prompt. On the other hand, the cast content was markedly reduced for several days; following a third injection of 4 dg. of arsphenamine the albumin was again markedly decreased for twenty-four hours, but returned to its usual level. After the fourth arsphenamine injection casts also became abundant again and no further improvement in the urine could be produced by either arsphenamine in small daily or



Fig. 1.

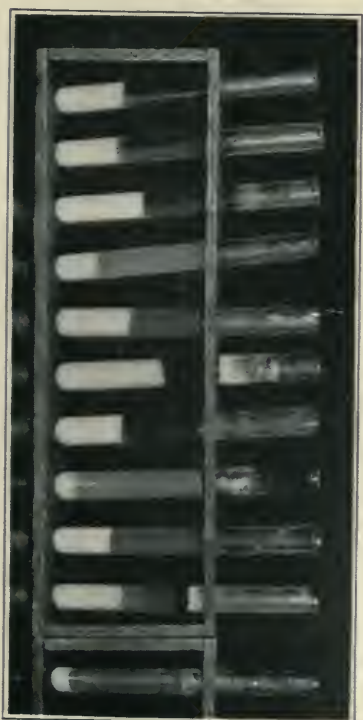


Fig. 2.

Fig. 1.—(Case 250104). A waxy cast containing double refracting lipoids, and several scattered lipid globules in the urine seen by polarized light. The Maltese cross in the brilliantly refractive globule is characteristic.

Fig. 2.—Series of tubes illustrating the Herxheimer-like wave in albumin content during the period of improvement under arsenphenamine. Tube 1 represents the average albumin content of the urine; Tube 2 the albumin content of a four-hour specimen just before the administration of 1 dr. of asphenamine; Tube 3 shows the increase in the next four-hour specimen; Tube 4 shows the definite drop during the second four hours; and Tube 5 the return to the usual level by the end of twenty-four hours. The next group of three tubes (Tubes 6, 7, and 8) shows the much more striking initial rise and drop that occurred during twenty-four hours following a larger dose of arsenphenamine (3 dr.), and the last group of three tubes shows the effect of 4 dr. of asphenamine. As after the preceding injections a complete relapse followed the improvement indicated by the last tube, and no further repetition of the improvement could be secured by either arsenphenamine or mercury.

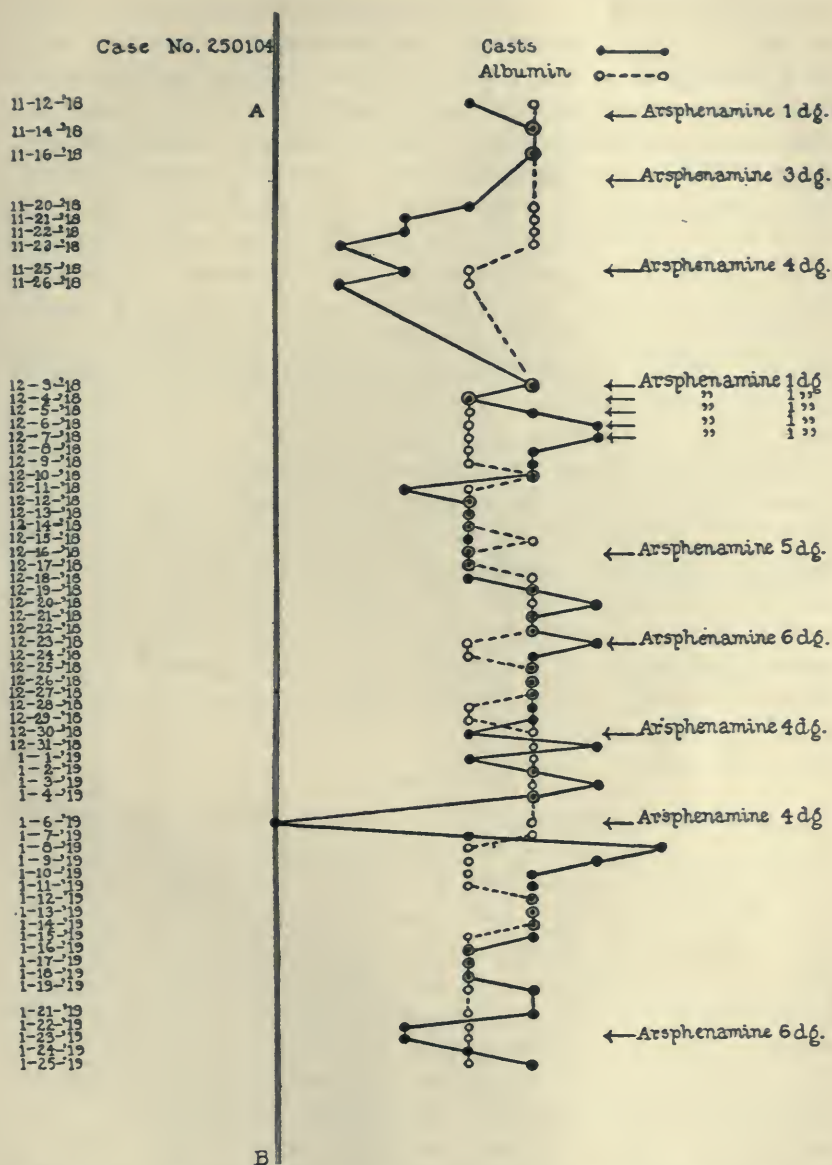


Fig. 3.—Chart indicating the albumin and cast content of the urine during two and one-half months' observation. The improvement in the cast content during the administration of the first three injections of arsphenamine paralleled the improvement in albumin content, but was more lasting, the albumin relapsing after twenty-four hours following each injection, and the cast content remaining markedly reduced in twenty-four-hour specimens for a number of days.

larger weekly doses, or by mercury succinimid intramuscularly. During three months of subsequent observation in the hospital the urine presented the picture of a chronic parenchymatous nephritis, with fluctuations which were never so marked, however, or of such long duration as those observed when the arsphenamine was first administered (Fig. 3). Blood pressure continued to vary, the systolic from 100 to 106, the diastolic from 67 to 80. The blood urea ranged from 12 to 22 mg. per 100 c.c. and the phenolsulphonephthalein from 50 to 55 per cent. The patient made a marked general improvement during his treatment. His pains disappeared, abdominal tenderness vanished, the neuroretinitis cleared up, and the pharyngitis disappeared. During the period between the first and second arsphenamine injections, when the urine showed the only definite improvement during the period of observation, he lost seven pounds in weight possibly due to loss of fluid, although there was no demonstrable edema or ascites at any time. After three months' observation, during which period another Wassermann test and a spinal fluid examination were negative, a staphylococcus was grown from a catheterized specimen, although there was little clinical evidence of a pyelonephritis; the patient was placed on vaccine treatment and discharged. Efforts to influence the nephritis by diet and by the removal of carious teeth and treatment of the pyorrhea while the patient was in the hospital were unsuccessful.

DISCUSSION

It is of course impossible to state definitely whether syphilis was a factor in the etiology of this parenchymatous nephritis. My personal inclination is to say that it was not. The tendency to relapse was apparent in my previously reported case.⁶ The response of the general condition in this patient and the clearing up of the pharyngitis and neuroretinitis under hospital care and treatment for syphilis can not be accepted as conclusive evidence of the presence of the disease. Stengel and Austin, who, after Munk, called attention to the increased frequency of occurrence of double refractive lipoids in the urines of syphilitics with parenchymatous nephritis, have not been able to propose this as a conclusive test. Therapy, therefore, remains the court of last resort in the decision as to whether or not a nephritis is syphilitic. Both Cole's and my experience⁶ agree with Hoffmann's, Munk's, and Audrey's that arsphenamine is the drug of choice for this purpose. The plausible history of recent syphilitic

infection, clinical signs of the disease of a suggestive but not conclusive type as in this case, double refractive lipoids, and an enormous albumin content in the urine, in view of the failure of the therapeutic test leave us with nothing more than a diagnosis of parenchymatous nephritis, failure of which to improve under prolonged anti-syphilitic treatment seems to show that it is not a true syphilitic process, but an incidental condition.

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AN ANALYSIS OF ONE HUNDRED CASES OF NEUROSYPHILIS

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THE following analysis was made in the hope that it might be of some aid in the early recognition of neurosyphilis. In obscure cases the question constantly arises as to whether the central nervous system is affected, for many cases of neurosyphilis are wrongly diagnosed, early in the disease at least, due either to a lack of knowledge of the symptomatology or failure to employ modern diagnostic methods. Some of these errors are directly traceable to a hurried examination in which the nervous system has been particularly neglected, and this applies especially to the examination of sensation, a field where the findings may be of the utmost significance.

One hundred random case records of neurosyphilis, mostly from the neurologic service of the University of Minnesota Hospital, were reviewed. In every instance one or more examinations of the spinal fluid¹ had been made, and these were positive in 86 of the cases in one or more of the four reactions. In those cases with a normal spinal fluid the diagnosis was made on the clinical evidence. In addition to the usual very complete history and physical examinations, the nervous system was examined in the large majority of cases by a neurologist.

TABLE I

	TABES	CEREBRO- SPINAL SYPHILIS	GENERAL PARESIS	MISC.	TOTAL 100
	(53 cases)	(32 cases)	(11 cases)	(4 cases)	
Males	39 or 73%	21 or 66%	8 or 73%	2 or 50%	70%
Females	13 or 27%	11 or 34%	3 or 27%	2 or 50%	30%
Denied					
Syphilitic					
Infection	27 or 50%	18 or 56%	6 or 54%	4 or 100%	55%

These cases are grouped as follows: 53 tabes dorsalis, 32 cerebrospinal syphilis, 11 general paralysis, and 4 miscellaneous cases. There were 70 males and 30 females. A history of syphilitic infec-

tion could be secured in less than half of the number. Where a positive history could be secured the date of infection varied from one to nine years before admission to the hospital; the free interval before onset of the first symptom varied from four months to thirty-five years, in tabes the interval averaging about ten years while in cerebrospinal syphilis it was much shorter, being less than six years. This same relationship held true as respects the severity of the illness, the tabetics not entering the hospital for a year or more after onset, while many cerebrospinal syphilitics entered in the first few months. Inadequate mental histories and the small number of cases prevent any conclusions regarding the parietic cases. Seventeen cases were wrongly diagnosed before admission and a lesson can be drawn from some of these errors. Nuzum² states that 8.7 per cent of tabetics have been subjected to laparotomy under mistaken diagnosis; that the crises are the main misleading feature, and that mistaken diagnosis occurs chiefly through failure to examine the nervous system. In this series, one tabetic with a history of abdominal pain and bloody stools, with lost knee jerks and a trabeculated bladder, was diagnosed "appendicitis, t.b.(?), and gastric cancer." Another with unequal pupils, superficial and deep sensory changes, and absent knee and ankle jerks was called "gallstones" on account of pain in the back. Two others with all the classical and text book signs of tabes were diagnosed "rheumatism." One tabetic, admitting diagnosis "chronic gastritis," is of particular interest as there had been a definite history of lead poisoning and the neurologic signs were not very clear-cut, but the spinal fluid showed a positive Wassermann, an increased globulin, 80 cells, and a gold curve of 1113311000. One of the tabetics had the not uncommon (unfortunately) experience of being twice operated for abdominal pain. Other admitting diagnoses of this group were heart, chronic appendicitis, abdominal obstruction, and hypertrophied prostate. One case of cerebrospinal syphilis with practically every part of the nervous system showing some objective finding was called "hysteria," and another, on account of chest pains, had been treated in a tuberculosis sanitarium, while two others were admitted as "diarrhea" and gastric ulcer." Three parietics were diagnosed respectively as "bulbar paralysis," "for study of back pain," and "tumor of right ovary and gallstones."

An attempt was made to classify the first symptoms complained of (Table II). In those instances where several complaints appeared at

approximately the same time the most prominent was chosen. Pain, from a dull aching character to lightning pains and crises, was by far the commonest symptom occurring in over 50 per cent of all cases. The site of election was particularly the abdomen and legs in the tabetics, but more common in the head in the cerebrospinal cases. Schaller³ found in tabes that pain was the most frequent symptom and head-

TABLE II

FIRST SYMPTOM	TABES	CEREBRO- SPINAL SYPHILIS	GENERAL PARESIS	MISC.	TOTAL 100
	(53 cases)	(32 cases)	(11 cases)	(4 cases)	
Pain:	31	13	3	3	50
General	(2)		(1)		(3)
Back	(1)	(3)	(1)		(5)
Head	(2)	(6)	(1)		(9)
Arms	(2)				(2)
Chest	(2)	(1)			(3)
Abdomen	(12)	(2)		(1)	(15)
Legs	(10)	(1)		(2)	(13)
Difficulty in walking	5	1	1		7
Ptosis		2			2
Double Vision	1				1
Failing Vision	1	1			2
Bladder Difficulty	2		1		3
Hemiplegia		2			2
Convulsions		1	1		2
Loss of Consciousness	1				1
Paraplegia		1			1
Tremor of Extremity	1				1
Speech Difficulty			1		1
Numbness of					
Extremities	1	1			2
Vertigo	2	2		1	5
Nausea and Vomiting					
(no pain)	2				2
Failure of Memory	2		2		4
Nervousness		1	1		2
Lassitude		5			5
Lack of Will Power	1				1
Loss of Sexual Power		1			1
Other Complaints	3	1	1		5
Symptoms preceded by trauma	4	2	3		9

ache was also common and that this frequent and constancy of pain was a proof of the radicular or meningeal origin of the symptom. Lucke⁴ in a very exhaustive study of tabes found that lancinating pains, staggering gait, sphincter and sensory disturbances were among the earliest symptoms. Difficulty in walking was complained of first

by only 1 per cent of tabetic cases, while lassitude (general tire and weakness) was the next commonest complaint in cerebrospinal syphilis. The remaining symptoms are pretty well scattered. It is interesting to note that 9 per cent of the total cases gave a history of trauma as the exciting cause of their symptoms.

TABLE III

SECONDARY COMPLAINTS	TABES	CEREBRO-SPINAL SYPHILIS	GENERAL PARESIS	MISC.	TOTAL 100
	(53 cases)	(32 cases)	(11 cases)	(4 cases)	
Pain:	21	17		2	41
General	(4)				(4)
Back		(1)			(1)
Head	(1)	(8)		(2)	(11)
Arms					
Chest		(1)			(1)
Abdomen	(8)	(5)			(13)
Legs	(8)	(2)			(10)
Girdle Sensation	8	1			9
Difficulty in Walking	20	6	2	1	29
Ptosis	1				1
Double Vision	1	2	1		4
Failing Vision	7	5	1		13
Hemiplegia	1	1			2
Paraplegia		1			1
Paralysis and Atrophy of an extremity	1	2			3
Tremor of Extremity	1	2			3
Bladder Difficulty	17	6	3		26
Speech Difficulty	4	2	3		9
Loss of Consciousness	1	5	2		8
Epileptiform		(4)			(4)
Apoplectiform		(1)	(2)		(3)
Numbness of Extremity	7	1	1	1	10
Vertigo	4	5	2	1	12
Failing memory	1	5	1	1	8
Other Mental Symptoms		1	3		4
Nervousness	3	2	1		6
Lassitude	6	2			8
Weakness of Legs	6	1			7
Charcot Joints	2				2
Decrease or Loss of Sexual Power	10	1	2		13
Increased Libido	1	1			2
Other Complaints	3		1	1	5

Table III shows the secondary complaints. Here again pain is the most prominent symptom but close to it comes difficulty in walking (38 per cent in tabetics and 19 per cent in cerebrospinal syphilitics);

26 per cent of all cases have some bladder difficulty, and this is about equally prominent in each group. Impaired sexual power, numbness of the extremities, girdle sensations, failing vision, weakness, and lassitude, are the next most frequent complaints in tabes. In cerebrospinal syphilis failing vision, failing memory, loss of consciousness, and vertigo are the next most prominent symptoms, while paretics gave a history of mental symptoms and speech difficulties.

In analyzing the objective physical findings (Table IV), the pupillary signs, sensory changes and abnormal reflexes are the most frequent. Baar⁵ emphasizes the fact that, as 18 per cent of normal cases show irregular pupils, it is not the size but the function of the pupil that gives the clew. The importance of the sensory findings in neurosyphilis, and especially in tabes, has been clearly brought out by Holmes,⁶ Patrick⁷ and others, and although this series does not show it, the loss of the ankle jerks in tabes may precede by some time the impairment of the knee kicks, due to the early involvement of the sacral cord.⁸

The four cases in the miscellaneous group were diagnosed, on discharge from the hospital, respectively chronic bronchitis, chronic neuritis (sciatica), intestinal ulcer, and senile dementia, and were included in this series on account of their neurologic signs and spinal fluid findings. Three of them had pupillary findings, not marked, to be sure, knee kicks were unequal or absent, and the spinal fluid in all four cases was normal as regards the cell count, Wassermann, and globulin, but did give colloidal gold curves, the senile dementia in the paretic zone and the others in the syphilitic zone (4442200000, 0012333210, 0013321000, 0013321000), and the complaints were pain, weakness, headache, and vertigo. Will these cases eventually develop more marked signs of neurosyphilis? Warwick and Nixon¹ have found that the colloidal gold reaction is the first reaction in the spinal fluid in many instances to appear, and in my opinion suspicious cases of the above types, unless they clear up promptly, should be put on anti-syphilitic treatment, or at least be kept under close observation, and the spinal fluid reactions followed. In support of this Barker,⁹ McLester,¹⁰ Haller and Waller,¹¹ and Baar⁵ emphasize the fact that syphilis is the cause of many obscure functional and organic nervous cases, and that the most frequent early symptoms are headache, irritability, dizziness, loss of memory, and slow speech.

TABLE IV

OBJECTIVE FINDINGS	TABES	CEREBRO- SPINAL SYPHILIS	GENERAL PARESIS	MISC.	TOTAL 100
	(53 cases)	(32 cases)	(11 cases)	(4 cases)	
Pupillary Signs:					
Unequal	6		1		7
Pin Point	4		1		5
R > L	10	14	5		29
L > R	16	12	4	1	33
Irregular in outline	40	21	11		72
Argyll Robertson	24	4	5		33
Sluggish to light	16	12	3	3	34
Springing	2	3			5
Consensual reflex lost	3				3
Impaired Vision	1	1			2
Optic Retinitis or Atrophy	1	2			3
Involvement of III, IV, VI Nerves	10	10	3	1	24
Ptosis	(3)	(4)			(7)
Nystagmus	(4)	(2)	(1)	(1)	(8)
Sensory Disturbance V Nerve	11	2	1		14
Impaired Function VII Nerve	1	4			5
Impaired Function VIII Nerve		3			3
Impaired Function XII Nerve	2	1			3
Hemiplegia		4			4
Other Impaired Motor Power of Extremi- ties	2	5			7
Atrophy of Extremity	2	2			4
Spasticity		5			5
Hypotonia	8				8
Incoordination upper Extremities	14	3	1		18
Ataxic Gait	6	2		1	9
Positive Romberg	19	2	3		24
Tremor of Extremities	2	2	3		7
Sensory Changes to Cotton and Pin	39	7	4		50
Upper Extremity	(10)	(2)	(1)		(13)
Trunk	(19)	(2)	(2)		(23)
Lower Extremity	(10)	(3)	(1)		(14)
Absent Calf Pain	14	1			15
Absent Testicular Tenderness	3				3
Impaired Vibration Sense	33	9			42
Upper Extremity	(16)	(2)			(18)
Lower Extremity	(17)	(7)			(24)

The nervous system may be involved in the very earliest stages of syphilis and yet give few or indefinite symptoms or signs.¹² No case should be discharged as cured without one or more spinal fluid examinations, not neglecting the colloidal gold reaction. However, a normal spinal fluid does not necessarily indicate a cure, in fact neurosyphilis can exist in absence of spinal fluid findings even when untreated,¹³ but the spinal fluid should be interpreted with the symptoms and physical findings. In doubtful cases of neurosyphilis a complaint of pain should put us on our guard and the nervous system

TABLE IV—Continued.

OBJECTIVE FINDINGS	TABES	CEREBRO-SPINAL SYPHILIS	GENERAL PARESIS	MISC.	TOTAL 100
Impaired Joint Sense	6	2	2		10
Upper Extremity	(6)	(2)			(8)
Lower Extremity	(17)	(7)			(24)
Charcot Joints	2				2
Reflexes—					
Elbow Jerks—unequal	2	6	1		9
Knee Kicks—absent	28			1	29
decreased	7	1		1	9
unequal	5	12	2	1	20
exaggerated		5	7		12
Ankle Jerks—absent	27		1	2	30
unequal	1	5	2		8
exaggerated		5	5		10
Abdominals—absent	9	4	1		14
unequal	2	2			4
Positive Babinski Reflex	2 (?)	6	3		11
Mental Symptoms	1	3	7		11
Speech Defects			3		6
Aphasia	3	2			2

should be thoroughly examined, paying particular attention to the eye signs, sensory changes, and state of the reflexes as well as to the reactions of the spinal fluid.

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ATYPICAL SYPHILIS OF THE NERVOUS SYSTEM

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THE usual diagnostic symptoms and findings are absent in a number of people who, fundamentally, are specifically infected, and it is sometimes difficult to determine the date and manner of the infection and, further, to determine the degree of positiveness of a specific disease. These cases properly, and probably, come under the head of nervous diseases, which are seemingly handed down from one's ancestors and which do not present any of the cardinal symptoms of even an atypical syphilis. And yet, behind it all, there is, apparently, a specific lesion or an inheritance of structure which is specific in type,—this in spite of the fact that in many of these cases the neurologic findings are incomplete and the serologic findings are indefinite. At least they leave one with the impression that a negative blood Wassermann is not sufficient. In a few instances where a patient has a positive blood Wassermann there is a negative spinal fluid Wassermann. This is a reversal of the expected serologic diagnosis. Commonly, the spinal fluid is where one expects to find the Wassermann reaction, the blood in these cases being either negative or doubtful. If one is to attempt to diagnose syphilis on a negative blood finding he must have something to corroborate his diagnosis. I think we pay too little attention to the type of individual who has syphilis, in some form, in some part of his body which is more or less in touch with his nervous system. We certainly do not analyze the individual as closely as we should, and at the same time keep in mind the possibility of an old syphilis.

In order to illustrate one point mentioned,—the lack of findings and the presumption of syphilis being present,—the case is presented of a woman of thirty-seven who, in all probability, has lived an exemplary life, and who married a man who was clean and without a probability of syphilis. Following an active child-bearing period she became weak, and easily exhausted, finally depressed, and then confused. After being confined to the bed for a few weeks she improved, and, although she had not recovered from her depression, she went

to a new home built purposely for her. The morning after her arrival there she was found in the bathroom, having made an attempt to end her life by thrusting a sharp-pointed mechanical instrument down her throat. She was rescued, fortunately, from an immediate fatality, but in removing the instrument a safety pin and a piece of wire, the wire was unprotected at both ends, must have dragged along the mucous membrane of her pharynx, and perhaps some of the surrounding parts. Very soon after this accident she developed a minor ptosis of one eye, a contraction of the pupil of the same eye, and a defect in the movement of her face on the same side. She was submitted to repeated examinations of both blood and spinal fluid, including the colloidal gold, the Wassermann, and the Nonne. The fluid from the spinal canal and the blood were sent to two different laboratories on two occasions, and each time the findings were negative. But on the assumption that she had a ptosis and a right pupillary defect she was put on intensive treatment (neosalvarsan), and was given mercury internally. She made a very prompt recovery in spite of the injury to her tissues by this sharp-pointed instrument. She first recovered her mental balance; and later her ptosis disappeared, the pupil again resumed its responsibilities, and she regained her full power in her face. The supposition is that this woman had a concealed syphilis derived from some unknown source, and that the injury she inflicted upon herself was the precipitating factor in the development of her physical findings.

A case somewhat similar as to the conclusions is that of a woman thirty-six years of age, who, four years ago, suddenly and without any special reason, became tired and depressed. Her depression lasted for a week or ten days, when she suddenly got out of bed and went down town, and made purchases far beyond her means and her husband's credit. She evidently had ideas of grandeur and extravagance, which ceased as abruptly as they came; and in a few weeks she had regained her poise, both mentally and nervously. She was then well for three years or more. In November, 1919, the family moved to a town in the West, and there endeavored to establish a home. A similar attack developed, that is, an attack similar to the one described above, characterized by tire and depression, grandiose ideas, and finally, a period of excitement. She was sent East to be placed in a hospital, traveling in a private car attached to a train going sixty miles an hour. In her confusion she walked out of the rear door of the car

and stepped off the rear end of the train, simply remarking to her husband, in passing, that she was going out to see one of the neighbors. She evidently fell, as a semiconscious person would fall, without resistance. She was rolled over between the tracks, and the train, going at such high speed, did not stop for two and a half miles; but when they backed up to pick her up she was walking toward the train. One tooth had been jarred loose, and she had picked it out with her fingers. She had numerous brush bruises and some cuts in her skin, but no bones were broken and there were no serious injuries. She arrived at the hospital in safety and was put through the usual tests. She was found to have a ++++ positive blood and spinal fluid Wassermann. The question that arises is whether a latent syphilis may not be fanned into an active stage by an accident or an injury such as this woman passed through. It is quite probable that had her blood and spinal fluid been examined four years ago, they would have presented the same findings, but it did not occur to any one in attendance to do this. It is one of the illustrations which show that latent or concealed syphilis is one of the things for which we must be constantly watching.

Many of our nervous cases presenting a chain of symptoms characteristic or at least resembling one of the classical symptom-complex disorders, may have for their base an old syphilis. The variability and the irregularity of sensation occurring in any chronic case, and particularly if it is associated with a general nervous and mental irritability, is a strong enough reason for investigating, by any known method, for the presence of syphilis. Skin diseases that accompany nervous disorders are not infrequently specific in their origin. It is well to remember, too, that syphilis of the nervous system is frequently accompanied by a disease of the meninges or the surface of the cord or brain. In these cases the multiple and irregular symptom group are usually quite sufficient to suggest a search for a specific infection, whether old or new. Many of our cases of so-called organic brain and cord lesions are typically specific, and yet, because of our belief in the clean life of the individual, we sometimes forget that syphilis is something to be reckoned with. Unfortunately for us, however, this syphilis is of so long standing that it has invaded territories by new growth, and little or nothing can be done for these cases. This is well illustrated in Erb's syphilitic spinal paralysis, which is, in reality, only an initial stage of a chronic meningomyelitis due to syphilis. Then, too, the common or acute brain lesions, such as pal-

sies that are incomplete and varying in type and in severity, demand the same careful search for a specific history. A thickening of the membranes in any part of the brain or cord may be the only evidence of the presence of syphilis. The writer recalls, too, one case where multiple cysts developed around the area at the base of the brain, numbering sixty in all, due, of course, to an arterial syphilis; but this was not discovered until an attempt was made to tenotomize one of the eye muscles for a defect. Even though this operation was performed with care and skill it started up an inflammatory or exudatory process, which brought out the true cause of the ocular palsy, namely, syphilis. The man died within three days following this minor operation. This simply serves to emphasize the importance of keeping in mind, among our surgical patients, the possibility of syphilis as a factor in the development of the disease. It looks surgical, but should be left to the syphilologist.

The number of so-called functional nervous disorders, such as we are in the habit of calling neuroses, psychasthenias, and psychoneuroses, have syphilis as a causative factor, and doubtless many of these unfortunate and so-called simple "nervous" people have a real disease and need definite antispecific treatment rather than being left to go on wasting their lives and the lives of others in chronic invalidism.

It is hardly necessary to remind the readers that neither race, sex, nor profession should be considered in our investigation of a specific disease factor, and that no pains should be spared, either by direct questioning or other means, to get at the source of trouble. There is no use denying the possibility that even the clergy may be infected. But we, in our present methods, leave the patient to infer that we are not in any way suggesting that he has contracted syphilis, either deliberately or accidentally, and we simply smooth it over by satisfying ourselves that symptoms and laboratory findings are enough. This calls to mind, too, the suggestion made above, that there is a variability in the progress of symptoms which are due to syphilis. One patient complained, in 1907, of a coldness in his left calf during most of the winter. This disappeared in the spring, but returned the following winter. This time, however, it was accompanied by definite weakness of both knees. During the following year this weakness would alternate from one knee to the other, finally settling in the right knee, where it has remained. Then, too, there

developed in the right foot a slumping, flabby weakness of the muscles, so that the patient wore out the toe of his right shoe. Two years later the patient had some diplopia, but at the time he was examined the diplopia had been absent for two years. At the time of his entrance into the hospital he had difficulty in walking, and was obliged to use a cane. He gradually developed difficulty in reading, and an inability to get out the second half of a word. Bladder symptoms began without pain in any part of the body. A careful examination as to sensation showed there was practically no difference on the sides, in the two legs, although the patient said he noticed a difference in sensation. His reflexes were all in good order. The pupils were equal and reacted to light and accommodation. He had a double ankle clonus and ++ patellar reflexes. He had a positive Romberg symptom and an ataxic gait. Why look further for a diagnosis? It was proved, the man was put under treatment, and in four months he gained 50 per cent of the ground lost. This man might easily have been thrown into the ordinary spinal-sclerosis class, and yet, because his symptoms were variable and because he presented irregular and indefinite complaints, it was discovered that he was a typical case.

Then there is the oft-considered case of rheumatism which, under careful investigation, shows sufficient neurologic findings to put it in its proper classification. A woman, fifty years of age, came under observation. She had, after her marriage, two miscarriages, then two living children; following this she had twelve miscarriages, and then another healthy child. She considered herself well up to the summer of 1911, when she had some dental work done, after which she developed headaches, which were confined to the right side. These headaches were not accompanied by nausea, but were always worse at night. She had no disturbance of her vision or any loss of pupillary reflex except that the left pupil was larger than the right. Her headaches grew steadily worse, and finally, in the fall of 1911, she found that her tongue would not move freely and she talked badly. This disability entirely disappeared after a few hours, only to be followed three months later by another similar attack, but not so severe. At the time of the examination she was apparently as well as ever. She had no mental defects, there was no motor paralysis or anything of that sort, and the only complaint was that of pain in her head. The history further showed that her husband had "rheu-

matism'' below the knees, and that in the later years of their married life he became sexually impotent. This accounts for her condition, and no one would hesitate in arriving at the conclusion that the husband was the source of her specific disease.

A not infrequent attempt to diagnose suspected syphilis is to put our patients under treatment. This sometimes clears the atmosphere and enables us to make a decision. But in doing this we must remember that there are other toxic disorders that may be responsible, as illustrated by the nervous diseases which accompany diabetes and chronic nephritis associated with focal symptoms. Here, as a rule, the urinary findings will solve the problem. We must not overlook the arterial system, but must keep in mind that many arterial diseases are nonspecific in character. It is sometimes difficult, however, to separate arterial disease as specific or nonspecific, because of the uncertainty of these concealed forms, these protracted or latent types of syphilis. Neither must we overlook the mental states which are the outcome of specific infection. There are, undoubtedly, numbers of cases of depression and excitement representing other forms of psychosis due to specific infections and yet unrecognized for want of specific and definite examination.

It is a sad commentary upon the once partially civilized world that syphilization is taking the place of civilization, and that we may expect more and more of these indefinite types of syphilis of the nervous system, and, again, our problems will increase. But the frequency of syphilis, the commonness of it, and the probabilities of it should be a restraining factor in our diagnoses.

Note to the Editor

TO THE EDITOR:

March 30, 1920.

In reference to a short paper by Dr. Kolmer, "The Use of the Phrase 'Wassermann Reaction,'" American Journal of Syphilis, January, 1920, iv, p. 166, may I mention that I have been attracted to the term "Sigma Test" or "Sigma Reaction" which I understand is coming into use in France and elsewhere to stand for the phrase "complement-fixation test for syphilis."

The use of the Greek letter Σ has had some popularity instead of the word syphilis, lues, or specific. For exactness in reporting the Sigma test, the qualifying words, Wassermann, Noguchi, alcoholic antigen, cholesterin reinforced, etc., may be added. As the doctor who receives and is studying his serologic reports becomes better acquainted with the technical side of the reaction, he insists that the laboratory inform him of the method in use. It would certainly be confusing, as Dr. Kolmer notes, if some tests were reported "Wassermann test" which were based upon principles and technic very remote from the original.

The criticism that substituting the "sigma" for Wassermann would tend to accredit the test with specificity for syphilis can easily be disregarded, as those diseases which react positively and are not of syphilitic nature are infrequent, and those likely to meet with them could have in mind that frambesia tropica (yaws), leprosy (nodular form), and possibly sleeping sickness give the paradoxical positive.

Another criticism that is of more weight is that it is adding an unnecessary term to our nomenclature, and that the older and now well-known phrase "Wassermann test" will endure even as the word "salvarsan" has been deeply rooted as standing for the chemotherapeutic arsenic compound, which has been given the new American name "arsphenamine."

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Abstract of Current Syphilis Literature

It is the purpose of this JOURNAL to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Wm. H. Deaderick, Dugan-Stuart Bldg., Hot Springs, Arkansas.

WM. H. DEADERICK, M.D., EDITOR

SYPHILIS IN ARGENTINA.—M. Beatti. *La Semana Medica*, 1919, xxvi, No. 35, p. 235.

The author emphasizes that he did not often find syphilis in the patients whose blood and cerebrospinal fluid were examined by him, for among 2,400 Wassermann reactions which were studied, only 13 per cent of positive cases were encountered. There is a tendency to attribute arterial lesions invariably to syphilis. This supposition may be acceptable in a general way, for youthful patients, but a study of comparative pathologic anatomy serves to show the existence of these vascular affections in cattle, sheep, and horses, where syphilis has never been held responsible for these lesions. The existence of concealed syphilis in Argentina is, of course, undeniable, and it is therefore recommended that an exploratory Wassermann reaction should be taken, when occasion presents, especially in adult patients. The author's object is to point out that cases classified as syphilitic are not very common in his country, according to his observations in careful control examinations, which were confirmed later on by the clinical findings.

EXPERIMENTAL SYPHILIS IN THE RABBIT.—Wade H. Brown and Louise Pearce, New York. *Journal of Experimental Medicine*, 1920, vol. xxxi, p. 475.

A study was made of the infections produced in rabbits inoculated in the testicles with two strains of *Treponema pallidum* which had been carried in rabbits for several years. Infection resulted in all instances; the incubation period varied as a rule between two and six weeks and under properly chosen conditions could be reduced to approximately three weeks or less. The resulting infection pursued a typically cyclic or relapsing course which affected both the spirochetes and the associated lesions in the testicle. The spirochetes in the local lesions exhibited periodic changes less marked and less regular

but identical in character with the changes which occur in the blood in cases of relapsing fever. The lesions in the testicle also showed periods of active development and quiescence or regression which followed closely upon the changes exhibited by the spirochetes. The specific reaction in the testicle showed considerable variation in the speed and sharpness with which successive phenomena occurred as well as in the character and extent of the processes themselves. These reactions were of two fundamental types. In one group of animals, the reaction was characterized by an intense cycle of acute exudation and infiltration with a lesser degree of proliferation, followed by crisis and subsequent recurrence of secondary cycles of proliferative reaction of a minor degree. In the other group of animals the reaction was more chronic in character and consisted largely of infiltration and proliferation. The progress of the reaction was more gradual, and sharp alterations in its course were absent. The infection progressed by a succession of stages with slight and irregular remissions. In a third group of animals the reaction was subacute, combining at the same time the processes of exudation, infiltration, and proliferation. The first cycle of reaction was fairly acute and terminated in a definite crisis with moderate regression, which in turn was followed by recurrence and more or less pronounced secondary cycles of proliferation. In all cases of outspoken infection, there was diffuse involvement of testicles, tunic, epididymis, and cord, but as the infection progressed, the lesions underwent many transformations, so that a variety of lesions was formed from processes which in the beginning were of a common type. Eventually, the reaction became more irregular and the infection became centered in one or more foci which were commonly situated in the epididymis, tunics, scrotum, or mediastinum testis. These centers served as residual foci of infection. The duration of the testicular process was found to be variable. In some animals the entire reaction consisted of but a single sharp cycle, and the local infection was terminated by crisis within four to six weeks after inoculation. As a rule, the period of active infection was from two to four months, and quiescent or inactive lesions not infrequently lasted for from four to six months. In exceptional instances local infection persisted for more than a year.

THE PATHOLOGY OF CONGENITAL SYPHILIS.—J. Frank Fraser, New York. *Archives of Dermatology and Syphilology*, 1920, vol. xxxviii, p. 491.

The case here reported is one to be added to those of apparently nonsyphilitic and immune mothers bearing children that have been proved syphilitic. From a review of antenatal pathology and embryology and the morphologic evidence in this case, as indeed in all cases of congenital syphilis, it would appear that infection takes place only

after the fetal organs have been formed—a fact which excludes the theory of germinal transmission unless we assume a practically unsupported theory of “larval inactivity” of the infecting organism. From the facts reviewed the most plausible explanation of the 5 per cent residue of nonsyphilitic and immune mothers of syphilitic children is that these mothers have a mild, low-grade form of syphilis.

THE SPINAL FLUID IN PRIMARY AND SECONDARY SYPHILIS.—Joseph McIver, Philadelphia. *Journal of the American Medical Association*, 1919, vol. lxxiii, p. 1765.

There is a slight increase of lymphocytes in the cerebrospinal fluid in the majority of cases of primary and secondary syphilis. The increase in protein content does not appear as early as the increase in lymphocytes. In this series not a single four-plus Wassermann reaction was obtained on the spinal fluid in primary and secondary syphilis. It does not seem reasonable to conclude that we can determine by the examinations of the cerebrospinal fluid in cases of florid syphilis just who is going to develop symptoms of the central nervous system.

SYPHILITIC NEURO-RETINITIS.—Major Harry Vanderbilt Wurdemann, Seattle, Washington. *American Journal of Ophthalmology*, 1920, vol. iii.

The writer has found in a large number of cases ophthalmoscopic evidence of syphilis, without other signs; and of the existence of which the patient was unaware, and this in recent years has been substantiated in every case by complement-fixation tests. Thus the ophthalmologist may become of great importance as a diagnostician. Every case of syphilis should have several ophthalmoscopic examinations and every case in which luetic lesions are found by incidental examinations of the oculist, should receive complete specific treatment.

NERVE DEAFNESS DUE TO CONGENITAL SYPHILIS IN THREE CHILDREN.—M. B. Kay, Pittsburgh. *Journal of the American Medical Association*, 1920, vol. lxxiv, p. 1162.

Each of these children was put on ascending doses of potassium iodide. Jan. 13, 1920, each child was taking 35 grains, three times a day. All of them were having the expected nasal discharge produced by the drug. One half grain of mercury with chalk, three times daily, very promptly caused gastric distress and was stopped for the time. All three children were brighter and were beginning to hear loudly spoken words. All could hear the ticking of a watch at a few inches; this they could not do when first seen. All were beginning to talk, using such words as mama, papa, yes, no, pie, and

a few others; and they were learning new words rapidly. When spoken to in a fairly loud tone, the children immediately paid attention, showing that they could hear. The first patient had grown one-half inch and had gained five pounds. The second patient had grown one-half inch and gained three and one-half pounds. The third patient had grown one and one-half inches, and gained four pounds. The general result had been good, but the question that must be answered to the parents is, What will be the final result? The author believes that little may be promised as to the recovery of the sense of hearing. Such patients show slight improvement if any, an irremediable damage having already been done by the time these patients are brought to one's attention. Further care of these children should provide for their education in a proper institution. They will also be put on inunctions of mercury, and the routine antisypilitic treatment will be continued to the time when repeated Wassermann reactions cease to be positive. The author believes it advisable to continue potassium iodide beyond this point, the guide, of course, being the improvement or failure of the sense of hearing.

CLINICAL PATHOLOGICAL STUDY OF AN UNUSUAL SYPHILITIC MANIFESTATION RESEMBLING JUXTA-ARTICULAR NODULES.—Herman Goodman, and William J. Young. *American Journal of Medical Sciences*, 1920, vol. clix, p. 231.

A case of multiple and symmetrical gummata of the tendons is described with the histological findings. Clinically the tumors closely resembled the tumors of juxta-articular nodules, but the histology is very different, and the two conditions could not be confused. Although the effect of antisypilitic treatment was not observed as the authors were both called to active service, the suggestive history, positive Wassermann, and histology of one of the lesions put the diagnosis of multiple gummata of the tendons on a sound basis. A search of the literature revealed no similar case, although mention of syphilis of the tendons was frequent enough.

ULCERATING GRANULOMA OF THE PUDENDA.—Herman Goodman, New York. *Archives of Dermatology and Syphilology*, 38, N. S. 1, 151, 1920.

Goodman reviews the literature, gives a bibliography, and personal observations of this disease as seen while on duty as venereal disease officer at Camp Las Casas, Porto Rico. Four cases were intensely studied, clinically, serologically, bacteriologically, and histologically. The recommended therapeutic agent, tartar emetic, was given but an inadequate trial. Clinical photographs are given, also the Calimato-bacterium granulomatis, the organism encountered in three of four cases, is pictured. The fourth case showed the Spirochete aboriginalis,

which is neither the *S. pallida* nor the *S. refringens*. Antisyphilitic treatment was given, but with no improvement in the lesions of ulcerating granuloma, although an accompanying condylomata lata in one patient was entirely healed, and the Wassermann reversed from four-plus to negative. Goodman is certain that the disease is not syphilis, although it may be associated with syphilitic lesions, or be present in a Wassermann positive syphilitic.

SYPHILIS AS AN ETIOLOGICAL FACTOR IN EPILEPSY.—David S. Booth, St. Louis. *Journal of the Missouri State Medical Association*, 1919, vol. xvi, p. 374.

The two cases reported appear identical save for recurrences in the latter case which evidently were due to discontinuing constitutional treatment, yet the former gave a four-plus Wassermann reaction of the serum while the latter was negative, though it is true the blood test was made after the patient had taken the iodide and mercury, the latter of which, however, had been discontinued sometime prior to the examination. Though some of the author's cases of epilepsy have shown only a two-plus Wassermann and a few but a one-plus reaction, he is treating them as though specific in origin with encouraging results, though it is too early to record conclusions. Those giving a one-plus Wassermann have been almost entirely children or women in whom he had reason to believe that if syphilis were present at all it was hereditary. While unprepared at this time to give data he is able to state that in his experience of the past several years the proportion of epileptics giving a Wassermann reaction in some degree is much greater than that given in available statistics and he feels confident that the laboratory has not detected all cases in which syphilis was, either directly or indirectly, an etiologic factor.

GASTRIC SYPHILIS WITH THE REPORT OF A CASE.—H. D. McGaughey and James I. Tyree, Joplin, Mo. *Journal of the Missouri State Medical Association*, 1920, vol. xvii, p. 21.

Examination reveals the patient to be under weight, but not cachectic, the emaciation does not keep pace with the reduction in red blood cells. There may or may not be buccopharyngeal findings, glands palpable. Reflexes are generally changed, tenderness in epigastrium, sometimes palpable masses, dependent on the duration of the gumma. Arteries unchanged, blood pressure not necessarily abnormal. Urine as a rule negative. Feces show mucus, pus and red blood cells. Stomach findings normal or of stagnant contents dependent on whether or not there is pyloric obstruction. There is a marked reduction in red blood cells and hemoglobin, 2,000,000 or less and 50 per cent. The Wassermann as well as spinal

fluid tests are in the large percentage of cases positive. Roentgen-ray findings in gastric lues outside of the ulcerative and hyperplastic types are not characteristic. It is only by combining the laboratory tests and therapeutic results with the roentgenologic manifestations that the lesions may be recognized. Malignancy, simple peptic ulcer, or the deformity due to a former ulcer, unless the sclerosis be well marked, must be taken into consideration. Generally speaking motility of the stomach is not involved to the same extent as in the other conditions which are up for differentiation. In the case reported the basis of diagnosis of gastric syphilis was: (1) Patient giving symptoms of malignancy but under cancer age. (2) Cachexia not in keeping with reduced red cell count. (3) Symptoms not painful enough for ordinary peptic ulcer. (4) One child with congenital syphilis, five miscarriages. (5) Positive Wassermann. (6) Blood cells and mucus in feces. (7) Roentgenologic findings, filling defect with absence of adhesions indicative of an organic lesion. (8) Therapeutic test, after six weeks' antisypilitic treatment patient's bowel movements have been reduced to two daily.

SYPHILIS IN HEART LESIONS.—Willard W. Dicker, Chicago. Illinois Medical Journal, 1919, vol. xxxvi, p. 235.

During the last year the author has made careful inquiry into the etiology of the decompensated hearts that have entered his service at the Cook County Hospital and has here listed those who entered during about five months of that time. There were 44 cases in all and of these 17 or 38 per cent proved to be syphilitic in origin, 10 or 24 per cent were rheumatic, 7 or 15 per cent were arteriosclerotic, 8 or 18 per cent were renal and 2 cases or 4 per cent were fatty hearts. The most apparent lesion is in the aorta. There is also, in a large proportion of cases an involvement of the myocardium which accounts for the failure of the heart to respond to treatment. The earliest symptom in many cases of aortitis is pain. This may vary from a transient sense of tightness or oppression about the upper sternum to the utter torture of true angina. The patients that have pain early are easily diagnosed, but many do not show this pain until rather late. The other symptoms are even more indefinite. Included, are such vague complaints as general debility, dyspnea, hoarseness, cough and slight cyanosis. Physical examination before the valves are affected gives only a slight increase in the aortic dullness and this is usually hard to make out. A clanging second aortic sound is described by some. Later on, of course, we get an aortic regurgitation and signs of aneurysm which makes the diagnosis easy, as it is of no avail as far as treatment is concerned. The x-ray gives us the most valuable information, for here we can detect very slight dilata-

tions. And of equal importance is a positive Wassermann reaction. Another point in the diagnosis is the therapeutic test and this will often give positive evidence. The study of the effect of syphilis on the heart must lead us to the conclusion that the heart of every so-called cured syphilitic should be very carefully watched throughout his life and any abnormality should call for active treatment.

A CASE OF SYPHILIS OF THE ANTERIOR HORNS.—George M. Goodwin, New York. *Journal of the American Medical Association*, 1920, vol. lxxiv, p. 387.

This case presented the symptoms of muscular atrophy and muscular fibrillation. Muscular fibrillations occur in conditions in which there is a degeneration of the cells of the anterior horns, of which the motor nerves are the axons. The diseases with which it is associated are: Chronic bulbar paralysis, syringomyelia, amyotrophic lateral sclerosis, and progressive spinal or neuritic muscular atrophy. The absence of bulbar symptoms and the retention of sensory discrimination ruled out the first two of these diseases. While cases are described of amyotrophic lateral sclerosis in which exaggerated reflexes and spasticity as the result of disease of the lateral columns occurred late or not at all, the condition is probably very unusual. The picture here seemed to correspond most accurately to that of progressive muscular atrophy, although the predominance of the atrophy in the leg muscles suggested the Charcot-Marie-Tooth type of progressive atrophy. The results of the laboratory investigations in this case were: The blood Wassermann reaction was one-plus. The spinal fluid showed a four-plus Wassermann reaction, a cell count of 80 with 92 lymphocytes in the smear, a positive globulin reaction, and a colloidal gold curve of the taboparetic type (22. 52. 532. 52. 51. 50. 5. 0.5). In the face of this evidence it was apparent that this patient was suffering from a syphilitic lesion of the anterior horns. In our own experience this has been a very rare manifestation of cerebrospinal syphilis, but the question arises as to what percentage of cases of progressive spinal atrophy will resolve themselves into this class with the application of the newer diagnostic tests for neurosyphilis. The patient is now under treatment with arsphenamine intravenously and autoarsphenamized serum intraspinally. He has had two such treatments with a diminution in the muscular fibrillation. The final result from the treatment will be reported later.

HEREDITARY SYPHILIS.—C. L. Barewald, Davenport. *Journal of Iowa State Medical Society*, 1920, vol. x, p. 14.

There is a general show, on first sight, of something not being just right. The voice may be weak, tiny, high-pitched. Perhaps you will hear the syphilitic cry; a high-pitch, strident outcry,

but weak and showing a sickly condition. Hiccough also may come under your notice, and is an unfavorable sign. The breathing may be accompanied with a wheezing sound. There may be snuffles, a catarrhal condition and exudate from the nose, of a seropurulent nature, mixed with some streaks of blood. The mother says it has a bad cold. A rash may show, or impetigo neonatorum; purpura hemorrhagica neonatorum, either under the skin, or as exudate, may come on; and that is always a grave symptom. The child is liable to succumb to white pneumonia. Children with bulla in the palm of the hands, or on the soles of the feet, have a very grave affection and never recover. Osseous cell proliferation about the joints, with exostosis and synovitis, give pronounced indications. Slow and painful dentition may be a result from the taint; although it may not. Then there may be many deficiencies; amongst which can be counted asymmetry in form, scantiness of hair, and wanting in patches, having no eyebrows, irregular features, generally enlargement of the spleen and of the liver; etc. In the beginning these signs and symptoms may not appear, or be scarcely appreciable. But from the third to the sixth month they become more marked and often give indubitable evidence of the hereditary syphilitic taint.

SOME OBSERVATIONS ON CONGENITAL SYPHILIS.—Robert Krost, Chicago. *Illinois Medical Journal*, 1919, vol. xxxvi, p. 172.

Most of the cases of fetal syphilis are born dead and may or may not show signs of syphilis externally. Of the cases born alive with signs of syphilis a pemphigoid eruption is occasionally present. In the infantile type the signs of syphilis appear in the majority of the cases during the first three months—most of them show lesions during the first month. The first symptom to appear in most of the author's cases was the snuffle. Because of the frequency of head colds in infants only those cases were classified as luetic snufflers where the snuffles had persisted for a number of weeks and was accompanied or followed by other symptoms. Next to snuffles the eruption was the most frequent initial symptom. The character of the eruption varied as to extent and form. The maculo-papular eruption was rarely found alone and the pustular was not seen. The papular form in infants is more apt to ulcerate and macerate and coalesce, due to the tender skin of the infant and also to the moisture present; this was especially noted in the diaper region. The typical skin lesions of congenital syphilis are not, however, these lesions mentioned—there are other lesions peculiar to congenital syphilis and found much more often. They appear as circumscribed or diffuse infiltrations of the skin found often around the mouth, forehead and cheeks, but more especially on the soles of the feet and the palms of the hands and in the gluteal region. The skin of the

affected area feels slightly thickened and stiff—it is shiny as though varnished over. The color depends somewhat upon its location; on the hands and feet it is dull or reddish brown, on the face frequently the color of a cigarette smoker's fingers. These affected areas are at first smooth, later they may desquamate after first showing irregular fissures. The skin frequently peels off, especially on the palms and soles and this process may be repeated. The hair of the scalp and eyebrows is often dry and sparse and comes out easily; alopecia may occur. The nails show many changes. The mucous membranes show linear ulcers around the mouth, these also appear around the anus. Mucous patches are found in the mouth, but not as often as in acquired syphilis. Condylomata are quite rare during infancy. The blood frequently shows a secondary anemia, at times very severe. Changes in the long bones are not very common in the infantile type. In the viscera the most frequent change was found in the spleen, which was enlarged in about 80 per cent of the infantile cases. Enlargement of the liver was frequent, but means little because so many things cause enlargement in babies. Changes in the nervous system are not rare, even during infancy, though not as frequent as later in life. Thus, in twelve cases, a noticeable bulging of the anterior fontanelle was present, due to varying degrees of hydrocephalus. Brain hemorrhage occurred in one baby at nine months of age and the child, now nine years old, is a typical hemiplegic. The special senses are not affected as often during infancy as later. The mucous membranes in late congenital syphilis are frequently affected, condylomata are more frequent than during infancy. The glands, even in the well-treated cases, show some hypertrophy and in untreated cases may show marked hypertrophy. The bones are frequently affected in late hereditary syphilis, either by gummata or by a hyperplastic osteitis or periostitis or both. These changes are most often found in the tibia, though they may be found in any of the bones. In the viscera, gummata appear most often in the liver. Some form of nervous disorder is frequent; it may be only excessive nervousness, at times choreic in form, it may be migraine or epilepsy.

SYPHILITIC AND TUBERCULOUS JOINTS.—Percy Willard Roberts, New York. *Journal of Orthopaedic Surgery*, 1920, vol. ii, p. 265.

There was abundant confirmation of the opinions expressed many years ago by Gibley, Ridlon, Whitman, Sayre and others that cases of joint syphilis cannot be distinguished clinically from tuberculosis. The author's experience leads him to go further than this and to say that the symptomatology and radiographic findings of these two diseases is usually so nearly identical that to make a diagnosis of tuberculosis joint disease without first eliminating the possible presence of syphilis invites serious error which jeopardizes the welfare of the

patient. The Wassermann test, upon which so much reliance is placed in the diagnosis of acquired syphilis, is of comparatively little help in the late manifestations of inherited lues. In forty-seven cases where symptoms subsided under mixed treatment and where often there was a positive family history and other stigmata of lues, Wassermann tests made with an alcoholic antigen gave eleven weak positives and thirty-six negatives. The same bloods treated with cholesterinized antigens gave thirty-three positives from one to four plus and fourteen negatives. The medical treatment of cases of this nature does not differ materially from that of acquired syphilis. The cardinal points are to crowd whatever drugs may be used to the limit of tolerance and to continue treatment for at least a year after all symptoms have subsided. There are two great dangers of relapse. One is the premature abandonment of vigorous therapy and the other severe trauma. The latter is always a menace, as children may feel perfectly well and be apparently normal long before their bone lesions are completely healed. The orthopedic treatment of these cases varies somewhat from that usually employed in tuberculosis as the goal aimed at is quite different. In tuberculosis a firmly ankylosed joint is generally desirable as tissue regeneration is not to be expected. In syphilis, on the other hand, replacement of necrotic bone areas may occur with the restoration of practical function. Therefore weight-bearing joints should not be maintained indefinitely in plaster casts and the patient allowed to walk. Removable braces which will prevent weight bearing and allow motion in the joints when the patients are lying down are preferable. So, also, are removable splints for the upper extremities, in order that voluntary motion at prescribed intervals may be carried out after the acute symptoms have subsided. Spine cases should, of course, be continuously immobilized until the radiograph shows solidification of the diseased bone. In fifty-one of the author's cases a diagnosis of tuberculosis had been made by twenty-six surgeons, and had been under treatment for from six months to twenty-five years, and yet all of them showed marked improvement under the use of mercury and potassium iodide and many of them became symptom free.

A NEW METHOD FOR PROCURING BLOOD FOR WASSERMANN TESTS.—
R. G. Owen and F. A. Martin, Detroit. *Journal of the American Medical Association*, 1920, vol. lxxiv, p. 98.

For the past three years the authors have drawn bloods for Wassermann tests with a special instrument which they have found convenient and economical. As shown in the accompanying illustration, it is a small metal cap which fits the centrifuge tube into which the blood is drawn. The sides of the cap are flexible so that it will fit tubes of varying sizes within a moderate range. A needle without a hub is sterilized by dry heat in a small test tube with

the point of the needle down. When ready for use the needle may be removed without touching the point. It is held by the middle, the wire withdrawn and the butt end of the needle is inserted into a hole in the top of the cap and tightened with a set screw. The cap is placed on the sterile centrifuge tube, and the instrument is ready for use. With this instrument, the tube and cap furnish a good handle, and the needle is held rigidly so that it may be guided accurately. The hole in the cap is made large enough to hold any size needle up to and including an 18 gage. In our work we use thick-walled centrifuge tubes, without a lip, whose outside diameter is approximately 16 mm. The needles used are either 18 or 20 gage. They may be purchased in gross lots for slightly less than five cents each. After use, the needle is dropped in a strong soap solution from which it may be cleaned with alcohol and ether, resterilized, and used many times. When the needles and tubes are sterilized in large lots, numerous bloods may be drawn within a very short time and at a slight cost, particularly if the needles are cleaned and used again.

THE OVER-VALUATION OF THE WASSERMANN REACTION.—Umbert. *Revista Española de Medicina y Cirugía*, 1919, vol. ii, No. 15, p. 477.

Summary: The Wassermann reaction has been overvalued in a number of cases. It does not permit the recognition of the existence of syphilis during the greater portion of the stage of second incubation, namely, at the decisive moment for the institution of inhibitory treatment. This inferiority is so much the greater because reliable results are obtained in this stage by means of the demonstration of the treponema. After the onset of the secondary or septicemic stage, the Wassermann reaction is superfluous, because the clinical symptoms are sufficient. As time goes on, the proportion of negative reactions increases, even in those cases where the existence of lesions recognizable by clinical means, indicates the continued activity of syphilis, as illustrated by a number of observations. In the tertiary forms, the reaction is likewise frequently negative in the blood, especially in tabes and in general paralysis—the value of the reaction in the cerebrospinal fluid being made much more considerable—as well as in aneurysms and the majority of cases of tertiary syphilis. All this is not surprising in a disease which immunizes the organism and in lesions which sometimes contain a small number of treponemas. Even the positive cases may prove misleading, especially in weak reactions, for these may appear in cases where no syphilis exists, either due to technical errors or to mistaken interpretation. The fundamental truth must be kept in mind that all affections appearing in syphilitic individuals are not necessarily of syphilitic character, so that even in

case of a positive reaction, the clinical study of each patient must not be slighted. There are cases in which the hemolysis is incomplete and retarded; under these conditions, the reaction can be reliably interpreted only by a physician who has previously followed up the disease. Based upon these views, the author emphasized the necessity of attaching great importance to the clinical exploration, especially for the discovery of the first symptoms of visceral involvement, as well as nervous and vascular affections. The early manifestations are apt to be overlooked or not accorded the necessary importance. To render the diagnosis of an established hemiplegia or spinal paralysis is of no advantage to either the patient or the physician, and it makes little or no difference if the reaction is positive or negative, seeing that there is no remedy for the disease. On the other hand, a physician who knows how to examine and who understands the physiopathology of the symptoms, is able to foresee the imminence of the serious dangers and to prevent by his intervention the evolution of certain diseases which in many cases are more to be dreaded than death itself.

A PRELIMINARY REPORT ON THE USE OF A NEW ARSENICAL COMPOUND IN THE TREATMENT OF SYPHILIS "MON-ARSONE."—Commander B. L. Wright, M.C., U. S. Navy, Lieutenant L. A. Kennel, M.C., U. S. Navy and L. M. Hussey. *Medical Record*, 1920, vol. xcvii, p. 607.

From their investigations the authors believe they have demonstrated that the standard laid down for an ideal arsenical compound in the beginning of this paper has been fulfilled in Mon-Arsone. It is decidedly less toxic than the arsphenamin compounds as evidenced by the fact that 0.6 of a gram of arsphenamin, containing 186 milligrams of arsenic (2.8 grains), the maximum dose of this drug, frequently produces distressing and sometimes fatal reactions, while mon-arsone, in 2.4 gram doses, containing 1.064 gram arsenic (16.7 grains) has failed to produce a reaction or a toxic symptom of any description. Mon-arsone is perfectly soluble in small amounts of hot or cold water and may be administered in solutions in which each c.c. represents 200 milligrams of the dissolved solid without the slightest danger. Its singular property of having no hemolytic action upon the red blood corpuscles in this heavy concentration makes such a concentration unobjectionable. It requires no special apparatus for its administration. It contains approximately seven per cent more arsenic than arsphenamin. The solution of mon-arsone are so stable that they completely resist oxidation or decomposition when boiled or subjected to the higher temperatures and pressures of the autoclave. While mon-arsone is designed to be administered intravenously, accidental extravasation from the vein need not be feared, for from our premeditated subcutaneous injections of this drug and from

several accidental leakages from out the vein no untoward results have been noticed. These manifest advantages make it possible for any well qualified physician to administer this treatment as a routine office or bedside procedure, and render it possible for the naval and army surgeon to have this desired therapeutic agent at his command at all times whether at sea or in the field. Mon-arsone has passed all the requirements demanded for arsenicals by the Public Health Service, having successfully met the established tests prescribed, and made in the Hygienic Laboratory, Washington, D. C.

THE PRACTICAL VALUE AND UTILIZATION OF THE WASSERMANN TEST IN GENERAL PRACTICE.—Robert A. Kilduffe, Chester, Pa. *Archives of Diagnosis*, 1920, vol. xii, p. 125.

A positive reaction may be obtained within 8-10 days after the appearance of the initial lesion, though the results are more constant after an interval of three to six weeks. In untreated secondary lues, and in tertiary lues, the test is highly specific and of incalculable value. A single negative reaction does not by any means exclude syphilis. Where ground for suspicion exists, the test should be repeated, preferably after a provocative course of treatment. In cases of syphilis of the nervous system the spinal fluid should be examined, as the blood may give a negative reaction. While a positive reaction indicates syphilitic infection, it does not necessarily mean that the lesion from which the patient suffers is syphilitic. A tuberculous or malignant condition must not be overlooked as such because the Wassermann is positive. In obscure conditions a Wassermann should always be made, regardless of the history. Where abortions are frequent, a Wassermann may lead to efficient treatment and the saving of a child. The effects of treatment can and should be followed and controlled by repeated Wassermans. With special modifications of technic, the amount of syphilitic antibody present may be measured with marked accuracy. A single negative does not mean a permanent cure. It is safer to insist upon tests at intervals of three months for a year after treatment has been discontinued. The Wassermann test is the most constant single symptom of syphilis and should be resorted to in all cases where the diagnosis is not clear and evident. To secure the maximum results, choose a competent and accessible serologist and treat him as a consultant—the results will be highly satisfactory and of incalculable benefit in the diagnosis and treatment of a surprisingly large number of cases in every-day practice.

SILVER SALVARSAN AND THE WASSERMANN REACTION.—W. Schönfeld and G. Bienbaum, *Münchener medizinische Wochenschrift*, 1919, vol. lxvi, No. 38, p. 1087.

Although the favorable effect of silver salvarsan upon the clinical manifestations is generally conceded, opinions vary as to the behavior of the Wassermann reaction, and the authors proceeded to the exam-

ination of the new remedy from this point of view. Silver salvarsan has been in use in the Würzburg University Clinic for Skin Diseases, since November, 1918, and over one thousand injections have been administered up to the time of the report. A complete course of treatment was given in 67 cases of syphilis, including 30 men and 37 women. The majority of these patients were treated with silver salvarsan alone, 51 in number; a few patients received silver salvarsan and mercury simultaneously. The results may be summarized as follows:

1. Silver salvarsan acts rapidly upon existing clinical manifestations, moderately upon glandular enlargements. As compared with other salvarsan preparations, it is superior to neosalvarsan and salvarsan sodium without mercury. It probably does not quite equal the efficiency of old salvarsan in its original dosage, but is evidently less toxic.

2. The effect upon the serological behavior is variable. Early syphilis with a positive Wassermann reaction and a recent onset of the disease, becomes negative on an average in two-thirds of the cases, after six weeks; in one-third of the cases, the Wassermann reaction persists in spite of the treatment. General syphilis of long standing, with a positive Wassermann reaction, proved refractory to the dosage employed by the authors (11 to 12 injections within eight to twelve weeks, total dose 2.95).

3. Of transitory side-effects, the angioneurotic symptom-complex is the most common manifestation, more common than with neosalvarsan and sodium salvarsan, and also than with old salvarsan. Persistent side-effects or permanent injuries were not observed in the authors' experience. A fundamental difference between the side-effects of the older salvarsan preparations (eruptions of variable degree, thromboses, and so forth) could not be demonstrated.

4. In long-standing cases of syphilis, a combined mercury treatment is still to be recommended, or alternate treatment with mercury and silver salvarsan, respectively, in suitable cases.

The dosage of silver salvarsan is approximately as follows, taking into consideration the age, sex, and other physical conditions, such as weight: Men receive as the first two or three doses 0.1-0.2; women receive 0.1-0.15; followed by five or six injections of the corresponding maximum dose, amounting to 0.3-0.35 for robust men, and to 0.2-0.25 for robust women. Next follow three to four injections at intervals of about six days with a dose of 0.25 for men and 0.2 for women; so that the average total quantity in a course of ten to twelve injections amounts in men to about 2.5-2.75 and in women to 2.0-2.5. In a number of cases, these quantities were exceeded, whereas in others they were not entirely reached. The customary precautionary measures which have to be observed after the injection of the older salvarsan preparations are even more necessary when the new remedy is used, such as rest after the injection, and no injection shortly after a meal.

TREATMENT OF SYPHILIS WITH SILVER SALVARSAN.—L. Hauck. *Medizinische Klinik*, 1919, No. 24, p. 581.

In a series of six hundred injections which were administered in the Erlangen clinics, no serious disturbances due to the remedy were noted. Associated manifestations were found to be more common in women than in men, and occurred in the form of rise of temperature, headaches, vasomotor disturbances and vomiting. Damage to the internal organs was not produced in any instance, and no toxic cutaneous eruptions were observed.

BAD RESULTS OF SILVER SALVARSAN IN A CASE OF FLORID SYPHILIS.—Riecke. *Medizinische Klinik*, 1919, No. 14, p. 329.

In the course of treatment, in the form of administration of 1.3 silver salvarsan within forty-two days, through seven intravenous injections, universal dermatitis appeared, with excoriation and crust formation, under symptoms of severe prostration, psychic and motor unrest, as well as a marked rise of temperature. After these phenomena had visibly subsided, the patient died as the result of pneumonia. The author explains the severe manifestations as due to general damage of toxic character.

HEMOLYTIC ACTIVITY OF SOLUTIONS OF ARSPHENAMIN AND NEOARSPHENAMIN.—John A. Kolmer and Elizabeth M. Yagle, Philadelphia. *Journal of the American Medical Association*, 1920, vol. lxxiv, p. 643.

All solutions of arsphenamin are hemolytic, owing primarily to the direct hemolytic activity of arsphenamin itself. Solutions of arsphenamin in isotonic saline solution are from three to ten times less hemolytic than solutions in water. (The hemolytic activity of solutions of arsphenamin in water and isotonic saline is unavoidably increased by the addition of sodium hydroxid for the purposes of neutralization; the addition of an excess of alkali increases hemolytic activity. Concentrated solutions of arsphenamin in water and isotonic saline are more hemolytic than dilute solutions. Nearsphenamin is not hemolytic. Dilute solutions of nearsphenamin in water, as 0.9 gm. in 90 c.c. or more of water, are hemolytic, owing to hypotonicity of the solution. Concentrated solutions, as 0.9 gm. in 30 c.c. or less of water, are not hemolytic, owing to the presence of sufficient inorganic salts from the drug to render the solution approximately isotonic. To avoid hemolysis in the administration of dilute solutions of nearsphenamin, sterile physiologic sodium chlorid solution prepared of freshly distilled water should be used; when the concentrated solutions are administered (each 0.1 gm. dissolved in 3 c.c. or less), sterile water may be employed. The degree of hemolysis produced by the administration of arsphenamin may be lessened (a) by using instead

of water sterile saline solutions of such strength as to render the solutions isotonic; (b) by avoiding the administration of concentrated solutions; (c) by carefully neutralizing and "clearing" the solution with sodium hydroxid, counting the drops or otherwise measuring the amount necessary, and adding not more than a fifth of this amount in excess, and (d) by giving the injections slowly so as to permit gradual mixing and dilution of the solution with the blood.

EXPERIENCE WITH SODIUM SILVER SALVARSAN.—R. Lenzmann.
Deutsche medizinische Wochenschrift, 1919, No. 13, p. 355.

The author summarizes his findings as follows: (1) Sodium silver salvarsan is eminently adapted to utilization in the treatment of syphilis, because it is readily tolerated and in efficient doses possesses a much lower toxicity than other salvarsan preparations. (2) The technic of the injections is not so simple as that of the injections of neosalvarsan. It requires special attention and scrupulous observance of all the rules governing the intravenous injection of arsenobenzol. (3) The effect upon spirochetes living in active foci is remarkable, as can be demonstrated by means of dark-field illumination. Further observations will have to show whether the Wassermann reaction is more strongly influenced than by other arsenobenzols, and clinical experience is still required concerning its effect upon the spinal fluid. (4) Sodium silver salvarsan is extremely well tolerated by children. The author calls attention to its employment in scarlet fever, in which disease salvarsan preparations were recommended by him as long as seven years ago. Precisely in children, silver salvarsan is especially desirable on account of its slight toxicity.

TUBING AS A CAUSE OF REACTION TO INTRAVENOUS INJECTION, ESPECIALLY OF ARSPHENAMIN.—John H. Stokes and G. J. Busman,
Rochester, Minn. *Journal of the American Medical Association*, 1920, vol. lxxiv, p. 1013.

A certain widely distributed brand of so-called pure gum rubber tubing seems to contain, when new, a toxic agent responsible for a definite type of reaction following the intravenous administration of arspenamin, and possibly also of alkaline solutions and transfusion mediums. The toxic substance gradually disappears from the tubing on use. The toxic substance is apparently removable in the first instance by soaking the tubing for six hours in normal sodium hydroxid solution and rinsing. The toxic property is not destroyed in the ordinary process of sterilization by boiling (from one-half to one hour), is not soluble in water or removable by irrigation, appears in toxic amounts in arspenamin, neoarsphenamin and dilute sodium hydroxid solution merely on passing them through a new tube enroute from container to vein, and is not apparently associated with the

mechanically removable debris from the inner surface of the tube. The reaction induced by this agent, as obtained by the use of new tubing for intravenous injection of the substances mentioned, consists of chills coming on from thirty to sixty minutes after injection, with nausea, vomiting, diarrhea, a sharp rise of temperature, sweating, severe headache and lumbar cramps, emotional disturbance amounting at times almost to hysteria, and subsequent profound prostration. The reaction can be induced in typical form in dogs. The identity and toxicology of the poisonous principle are under investigation.

PARAPLEGIA AFTER ARSPHENAMIN IN A CASE OF RETROBULBAR OPTIC NEURITIS.—T. J. Dimitry, New Orleans. *Journal of the American Medical Association*, 1920, vol. lxxiv, p. 1150.

It is well to remember that syphilis presents a vagary of symptoms at times lacking a definite explanation. What appears as an incongruous syndrome both pathologically and clinically is very often to be made clear when syphilis is taken into consideration, and an appreciation of the changes that might occur from a syphilitic arteritis, better known as a Huebner arteritis. To rid ourselves of dissenting opinions in unclassical cases, it will be essential to find the spirochete present. Then we may emphatically state the existence of the syphilitic disease.

ARSPHENAMIN REACTIONS.—John F. Martin, Boston. *Journal of the American Medical Association*, 1920, vol. lxxiv, p. 1218.

Sequelae arising from arsphenamin medication may be thus classified: the incidents, slight untoward symptoms occurring in patients with normal tolerance to arsphenamin, such as vertigo, palpitation, disturbances of taste and smell, or slight nausea; the reactions, usually occurring in syndromes, and causing discomfort and sometimes incapacity, which may be ascribed to allergic or acquired susceptibility to arsphenamin, functional or organic complications, or toxic arsphenamin solutions; the grave reactions (sometimes fatalities), such as dermatitis exfoliativa, toxic jaundice, hemorrhagic encephalitis, and gangrene; the accidents, such as thrombosis, phlebitis, and infiltrations about a vein. With careful observance of all precautions in the administering of a properly prepared arsphenamin solution to a risk-free patient, if treatment is not too energetic, reactions may be reduced to a minimum, both in private practice and hospital clinics. Each patient, during a course of treatment, should be carefully observed as to individual susceptibility and tolerance for arsphenamin. Standard treatment may serve as a guide for the average case, but one must individualize to prevent reactions and best treat the patient.

THE TREATMENT OF SYPHILIS BY THE ANTISYPHILITIC SERUM OF QUERY.—J. Dobriansky, Vienna, J. H. Sequeira and Theodore Thompson, London. *Lancet*, 1920, vol. cxeviii, p. 903.

For this preliminary note on the treatment of syphilis by Query's serum cases have been selected with prominent symptoms of the tertiary stage which have proved resistant to the recognized methods of treatment. The manner in which these intractable symptoms have been at once relieved by Dr. Query's serum is most striking, and, in the authors' opinion, the serum deserves a thorough further trial in the treatment of the tertiary stage.

LABORATORY AND CLINICAL STUDIES BEARING ON THE CAUSES OF THE REACTIONS FOLLOWING INTRAVENOUS INJECTIONS OF ARSPHENAMIN AND NEOARSPHENAMIN.—Jay Frank Schamberg, John A. Kolmer, George W. Raiziss and Charles Weiss, Philadelphia. *Archives of Dermatology and Syphilology*, 1920, vol. xxxviii, p. 235.

The ingenious theory advanced by Danysz that intravascular precipitation of the organic arsenicals is the cause of the reactions (particularly the nitritoid reactions) after intravenous injection is only in part true. It explains the well-known precipitation of solutions of acid arspfenamin and probably also concentrated solutions of mono-sodium arspfenamin (i.e., arspfenamin neutralized to the point of clearing). There is no adequate evidence, however, that precipitation occurs after the use of disodium arspfenamin (hyperalkaline solutions), and there is no evidence at all that neoarsphenamin is ever precipitated in the blood. The mechanism which Danysz sets forth as the cause of the precipitation, namely, conversion of the sodium salt of the drug into the insoluble base through the interaction of the sodium salt with the carbonates, phosphates and other inorganic salts of the blood, is not supported by experimental evidence. Experiments carried out by us indicate that the phosphates of calcium, magnesium, sodium and potassium in the concentrations in which they normally occur in the blood, do not precipitate alkaline solutions of arspfenamin and neoarsphenamin *in vitro*, either when tested alone or in the presence of the other organic or inorganic constituents of the blood. Sodium bicarbonate alone forms a faint flocculation with minute amounts of disodium arspfenamin, but the precipitate dissolves readily on the addition of greater amounts of the latter. Acid arspfenamin precipitates readily in the presence of many of the organic salts of the blood; the precipitate, however, disappears when an excess of arspfenamin is added. Solutions containing even double the blood content of inorganic salts in an organic and protein menstruum ("artificial blood") do not form any appreciable precipitates with disodium arspfenamin *in vitro*. A faint flocculation which occurs occasionally with the first drop of arspfenamin, disappears when

the second drop has been added. Neoarsphenamin is not precipitated by any of the organic or inorganic salts of the blood. The authors believe that if arsphenamin is properly neutralized, that is, if the sodium and not the monosodium arsphenamin is injected, precipitation in vitro can scarcely take place. Experiments on the precipitation of arsphenamin with human blood in vitro yielded the following results: (a) Acid solutions of arsphenamin in a concentration of 0.25 per cent or more will precipitate in the presence of human serum in vitro. (b) Disodium-arsphenamin is not precipitated. (c) Monosodium arsphenamin is precipitated when added in very small quantities to human serum, the precipitate clearing on the addition of larger amounts, doubtless owing to the contained alkali. (d) When arsphenamin is dissolved in physiologic salt solution instead of distilled water, the results are not appreciably different. (e) Neoarsphenamin, even in 40 per cent solution is not precipitated in the presence of human serum. Experiments carried out on the hemolytic activity of arsphenamin and neoarsphenamin demonstrate that: (a) Both acid and alkaline solutions of arsphenamin are strongly hemolytic for defibrinated blood. The use of physiologic salt solution does not especially influence the results. (b) The hemolytic activity of arsphenamin varies with its concentration, but is not proportional to it. (c) Neoarsphenamin dissolved either in water or in physiologic salt solution, in concentrations ranging from 2 to 4 per cent, is not hemolytic for defibrinated blood. The fact that arsphenamin is hemolytic in practically all of the concentrations in which it is employed and that neoarsphenamin is not hemolytic except in very dilute solutions (0.9 gm. in 180 c.c. of water) or in extremely concentrated solutions (0.9 gm. in from 2 to 3 c.c.) sheds a degree of illumination on the relative manner in which these drugs are clinically tolerated. Another fact of importance is the hydrogen-ion concentration of these two compounds. The hydrogen-ion concentration of neoarsphenamin is 7.0 to 7.4 which is approximately that of the blood. That of acid arsphenamin is 4.7, while the alkaline solutions are beyond 9. The injections of acid solutions of arsphenamin are prone to produce death, or if less concentrated, may lead to the development of a bronchopneumonia as a result of intravascular precipitation of the drug. Concentrated monosodium arsphenamin solutions may, under certain conditions, likewise cause death, or in the event of recovery cause an embolic bronchopneumonia. The authors have no knowledge that pneumonic symptoms have ever developed after the use of disodium arsphenamin, nor after the use of neoarsphenamin. The injection of cloudy or turbid solutions of neoarsphenamin will almost invariably give rise to severe nitritoid symptoms in which syncope and shock-like collapse are the outstanding features. No pulmonary symptoms follow. Neoarsphenamin (and of course arsphenamin) should never be administered unless the solution is perfectly clear. Nitritoid re-

actions may at times follow injection of a clear solution of neoarsphenamin. As neoarsphenamin is never, in the authors' opinion, precipitated in the blood, the elucidation of the cause of such reactions must be sought elsewhere. Their studies lead the authors to reiterate the view previously expressed by them that the nitritoid reactions are related to some inherent property of the drug. In no other manner could the variation in the incidence of reactions with different lots and different brands of the drug be explained. They believe the cause to be traces of an unidentified impurity which for purposes of convenience and easy reference, they have designated Substance X.

THE FUNCTIONS OF THE CEREBROSPINAL FLUID.—Francis X. Dercum, Philadelphia. *Archives of Neurology and Psychiatry*, 1920, vol. iii, p. 230.

The cerebrospinal fluid is preeminently a fluid for the hydraulic suspension of the brain and cord; its function is essentially hydrostatic. Its chemical constitution is essentially that of the innocuous three quarter per cent common salt solution of the histologic laboratory. It has no action on the tissues with which it comes in contact: it is absolutely neutral and negative. It is distributed through the ventricles and subarachnoid spaces. It has no relation to the perivascular, pericapillary or perineuronal spaces. It possesses no function of and plays no role in nutrition. The nutrition of the brain and cord takes place as does that of the other tissues—through its blood vessels, the perivascular spaces playing the same role as do the perivascular lymph spaces in the other organs and tissues. The old belief that the brain and cord have no lymphatic system must be abandoned. The cerebrospinal fluid has its source in the choroid plexuses and perhaps in the general serous surfaces of its containing cavities. It leaves the subarachnoid spaces of the cranium by passing through the arachnoidal villi into the venous current of the sinuses; also to a lesser extent by the lymph sheaths of the cranial nerves; from the spinal subarachnoid space it passes out by the lymph sheaths of the spinal nerves. Attempts at medication of the brain and cord through the subarehnoid space, as in the Swift-Ellis method, are unscientific, as substances introduced into the cerebrospinal fluid rapidly disappear by passing out through the arachnoidal villi and the lymph spaces without in the slightest degree penetrating the nervous parenchyma; the beneficial exects hitherto ascribed to the Swift-Ellis and kindred methods are due entirely to the incidental spinal drainage. Medication of the nervous parenchyma must be attempted through the alimentary tract, through the skin, through the areolar tissue, or directly through the blood. A reemdy should be sought the ions of which will readily osmose through the capillary walls. Spinal drainage is urgently indicated in tabes and paresis for the reasons enumerated in this paper.

THE INTRASPINOUS TREATMENT OF NEUROSYPHILIS.—Charles R. Humbert, Kansas City, Mo. *Medical Record*, 1919, vol. xevi, p. 726.

Massive doses of one drug with sudden shifts to others in order to prevent the organisms from gaining a tolerance is the object sought. The patient is placed on the table, salvarsan is made ready, then spinal drainage is instituted. This decreases the already increased pressure in the cerebrospinal fluid, permitting both mechanical and physiologic passage of the drug through the chorioid plexus and meninges before it is taken up by the body cells. The salvarsan is now administered intravenously. Wait a reasonable length of time for the "reaction." If it occurs draw off the blood then; if not, draw it off just the same and administer the serum intraspinally in the usual manner. The circulation of the cerebrospinal fluid makes subdural and intraventricular injections unnecessary. Mercury is now started and pushed to the limit. Inunction, in the author's opinion, is the mode of administration, giving best results and causing no pain. The patients who are able are lined up in a circle; each rubs the one in front. There is a mistaken idea among too many physicians that in order to get the effects of mercury a few teeth, and occasionally portions of the mandible, must go. This is nothing short of malpractice. When there is evidence of salivation the blood is drawn and mercurialized serum is administered. The procedure is repeated until desired results are accomplished. The administration of iron, quinine, and strychnine tends to ward off the bad effects of the treatment. Throughout the course of treatment intraspinal injections are administered, as often as shifts to the other drug are indicated, provided the physical condition of the patient permits. The number of cases treated thus far are not ready for report. Results, however, have been so satisfactory that I felt a preliminary statement justifiable. Many men object to this treatment on grounds that it is too drastic for the patient. It is not nearly so much so as the inevitable. The statement that the intraspinal treatment possesses nothing superior to the time-honored intensive method is not borne out by experimental or clinical data.

OBSERVATIONS ON THE SPORULATION OF SYPHILIS ORGANISM AS SEEN ON THE DARK GROUND.—C. Lundie, Glasgow, Scotland, and F. H. Goss, Leeds, England. *Lancet*, London, 1919, vol. excvii, p. 1025.

Twice within a week of dark-ground work what was taken to be phagocytosis of a spirocheta by a leucocyte was observed, and on the second occasion demonstrated to a colleague. Subsequent observations, coupled with statements made by McDonagh that phagocytosis never takes place with *Spirochæta pallida*, have sug-

gested another interpretation of the phenomenon thus twice observed. On June 30th last their attention was called to a "leucocyte" which had burst and was pouring forth hundreds of the small refractile bodies so often seen in previous smears. The observation was confirmed and the appearance compared with Phase 36 of the life-cycle of the leucocytozoon syphilidis represented by McDonagh in Plate 11 of his book "Biology and Treatment of Venereal Disease." On a following occasion sporulation was observed with the dehiscent opening in front view instead of in profile as on the former occasion. Drawings were made of the appearances seen on the occasion. The lights and shades are made as seen in the dark ground, so that the dark spots in Figs. 2, 3, 4, and 5 are the points of dehiscence, as is confirmed by the fact that the flow of spores was always from these points. Fig. 6 was darker as seen in the dark ground than the brilliantly illuminated spores, but not so dark as the points of dehiscence. It seems to correspond to a developing free sporoblast (No. 38 in McDonagh's life-cycle). In view of the obvious sporulation thus personally observed in the dark field, and McDonagh's description of a life-cycle accomplished inside a leucocyte or endothelial cell, the phenomenon observed by them and once seen and demonstrated by Levaditi (who described it as phagocytosis) may actually have been the act of impregnation by the male gamete (the *Spirocheta pallida*) of the female gamete inside the leucocyte. One other phenomenon has been observed. Twice a flagellate and actively swimming organism has been seen. On the second occasion Captain Goss fortunately watched it for some considerable time till movement ceased, finally bursting and pouring out numerous diplococcal bodies. A certain number of short, fine, few-spiralled spirochætes were also seen, but they were not observed to arise from any preexisting body, as were the single and double coccal-formed bodies. They were like miniature *Spirochete balanitidis*, and might correspond to No. 25 in McDonagh's cycle. Forms which seem identical with No. 25 in McDonagh's cycle have also frequently been observed, but their origin and evolution have never yet been seen.

UNMERITED DENTAL SYPHILITIC CHANCRE. REPORT OF CASE OF SYPHILITIC INFECTION CONTRACTED AT SITE OF TOOTH EXTRACTION.—
Herman Goodman, New York. New York Medical Journal, 1920, p. 183.

Goodman reports a case of a young officer who had a tooth extracted, and ten to fourteen days thereafter an ulcer appeared at the site of the extraction. A Wassermann taken was reported negative. Spirochete examinations were not conclusive. The ulcer healed with local treatment, only to recur. Later there were evidences of a generalization of the syphilitic disease, and a Wassermann taken was

strongly positive. The only point of entry was the ulcer of the gum. Treatment proved very satisfactory.

Of the 9058 extragenital chancres collected by Bulkley, only 37 were of the gums. Scheuer reported in 1910, 154 chancres of the gums among the 24,855 extragenital chancres he collected. It would appear that chancre of the gums is an unusual lesion.

RELATIONS OF SPIROCHETES TO PARALYTIC PROCESSES.—F. Jahnel.
Correspondent Blatt für Schweizer Aerzte, 1909, xlix, No. 33-34,
p. 1277.

The demonstration of spirochetes in the brain of paralytic patients has led to a series of extremely important and interesting pathologic discoveries. Spirochetes could be demonstrated in only one-fourth to (under dark-field illumination) one-half of the cases, neither were they more frequently demonstrable when brain punctures were made. The number of spirochetes in the individual cases is subject to great local and temporary fluctuations. The remissions in the disease are to be interpreted as intervals produced by the liberation of antibodies. Two types of distribution of the spirochetes can be differentiated: (1) Their localization in sharply circumscribed foci; (2) diffuse distribution. Seats of predilection are represented by the anterior portions of the brain, especially the frontal pole and the gyrus rectus. In view of the scarcity of spirochetes in many brains, it would not seem to be justified to insist upon their demonstration in all cases of paralysis; but it is a legitimate conclusion that they are present in every paralytic brain. The paralytic attacks are acute exacerbations, anatomically constituted by an enormous destruction of nervous tissue; from the parasitologic point of view, they are associated with a considerable and extensive proliferation of spirochetes in the brain, more particularly in definite cortical areas. Death in a paralytic seizure is not only a cerebral death, but also a spirochete-death. Paralytic seizures include not only epileptiform and apoplectic attacks, but also sudden loss of consciousness and other abrupt psychic exacerbations. In such cases, enormous masses of spirochetes are found in the brain, precisely as in the liver of a case of congenital syphilis. A remote action of the spirochetes upon other organs does not enter into consideration in general paralysis. Proof is altogether lacking for the assumption of a toxic effect. The spirochetes rapidly die in these cases. The findings are not affected by treatment with salvarsan. After febrile diseases remissions as well as exacerbations may occur in general paralysis. Upon the basis of a personal observation, the author is enabled to show that even a severe suppuration in the brain, as in purulent meningitis, has no effect upon the spirochetes, and that the hope of controlling general paralysis through the artificial production of leucocytosis, must be abandoned. The histologic change constitutes the end-result of the gradually pro-

gressive pathologic process, the spirochete-picture representing the momentary picture at the instant of death. Hence, the histologic findings must not be indiscriminately charged to the spirochetes which happen to lie in that particular locality. Presumably the tissue-reaction in paralysis is of delayed onset, just as the secondary manifestations of lues are preceded, about three weeks previously, by an inundation of the blood with spirochetes. The two modes of distribution can only represent different stages of the same process. In the blood vessels of the brain, spirochetes have been demonstrated, in all probability they penetrate through the vascular walls as a result of their active motility. Their multiplication in the brain, however, is suggested by the appearance of colonies, like swarming bees. No answer has been found as yet for the question why the spirochetes do not lodge in the other organs of paralytic patients. In sclerotic scar tissue or in pigmentations after healed cutaneous eruptions, the spirochetes may persist for years; such remnants show a tendency to excentric diffusion, and a similar regional migration of the virus probably also occurs in the paralytic brain.

The spirochetes are found only in the gray substance, occasionally arranged in very small foci of spherical shape. In general paralysis, the gray cortex is the unextinguishable and constantly renewed focus of infection, from which the parasites may get into the blood, but will again return from the blood into the nervous system. To the variable distribution of the paralytic process in different cases corresponds a localization of the spirochetes varying from case to case. The diffuse involvement is explainable by the repeated disseminations through which every locality is repeatedly attacked by spirochetes, in the course of the paralytic process.

INHERITED SYPHILIS OF ENDOCRINE SYSTEM.—R. Barthélemy. *Le Bulletin Médical*, 1919, vol. xxxiii, No. 41, p. 541.

The author discusses the part played by congenital syphilis of the internally secreting glands in the pathogenesis of dystrophic disturbances of congenital-syphilitic origin. Numerous cases are on record in which pathologico-anatomic findings have shown the predilection of syphilis for the glands of internal secretion. Lesions of the liver, which passes as the first of these glands, are too well known to require more than a brief mention. The treponema has been found in every endocrine gland, not exceptionally or in minute quantities, but repeatedly and often in extreme abundance, the proliferation of the parasite equaling or surpassing that seen in the liver. The lesions of the endocrine glands are not specific as a result of their localization, but manifest themselves here as elsewhere by the two reactions of the gumma and sclerosis. The gumma is rarely extensive, and gummatous lesions are often compatible with an apparently good condition of the neighboring paren-

chyma. Sclerosis is more common and more serious, because it is not circumscribed, the secreting parenchyma becoming strangled, as it were, by the cirrhotic process.

The clinical existence of glandular dystrophies caused by syphilis results in the first place from the study of the stigmata, and typical observations of infantilism, nanism and gigantism are to be found in the writings of French syphilographers (Fournier, Hutinel, and others). Osteomalacia, achondroplasia, certain cases of chronic rheumatic arthritis, are undoubtedly caused by an endocrine disturbance, aside from the affections, more particularly as regards chronic arthritis deformans in youthful individuals. Trophic disturbances of the teeth are related to these bony disturbances, hypoplastic dental lesions often depending upon glandular involvement in general and thyroid affections in particular. Other dystrophies or trophic anomalies referable to glandular lesions are represented by obesity (thyroid, genital, suprarenal, or pituitary origin); diabetes, chlorosis, and athrepsia, which in certain cases is probably due to a glandular instability amenable to specific treatment.

Endocrinic congenital syphilis undoubtedly exists, although its details are still imperfectly known because the pathology and even the physiology of the blood glands are incomplete, and because congenital syphilis is often misinterpreted. It suffices for our attention to be drawn to these facts for observations to multiply. The conclusion is already justified that the congenital-syphilitic dystrophies usually owe special features to endocrinic involvement and that the dystrophic stigmata are indebted to it for a part of their characteristics (for example, skeletal and dental stigmata). The toxic nature of congenital syphilis, as suggested by certain more or less inexplicable facts, is elucidated by the powerful action of the glandular products upon the nutritional equilibrium of the organism. The toxin, far from being of treponemic origin, is usually merely a vitiated or deficient endocrine secretion. The best proof of this is furnished by the hereditary cases of congenital syphilitic exophthalmic goiter, as reported by several observers, and is also shown in the form of endocrine deficiency, or functional weakness, of the suprarenals, for example. Under these conditions, individuals having congenital syphilis with histologic or even physiologic involvement of their endocrine glands, become the victims of severe disturbances as a sequel of trifling accidents such as mild ordinary infection or intoxication, harmless traumatism, etc., which are tolerated without any trouble by a normal organism.

All these remarks are applicable to congenital syphilis of the second generation, which may inherit not only the treponema, but its sequelæ in the form of a permanently damaged soil. The endocrinic lesion in the first offspring is no longer essential to developmental disturbances and nutritional impairment in the later

descendants of syphilitic ancestors. Congenital syphilis of the internally secreting glands is thus seen to be capable of producing a great variety of phenomena, of extremely variable degree. Many of the resulting conditions become established during extrauterine existence or at any rate, in early childhood, without prospect of a cure by delayed specific or even opotherapeutic treatment. The earliest possible intervention is therefore required in order to counteract as far as practicable the sometimes inevitable degenerative process.

SYPHILIS IN DISEASES OF THE HEART AND CIRCULATION.—Charles W. Chapman, London. *Lancet*, 1920, vol. cxcviii, p. 1004.

There are reasons for expecting visceral manifestations of syphilis to appear at an unusually early period in the case of those who have gone through the stress and strain of the late war. Cases of atheroma and tabes occurring thus early have already been reported, and it is fair to assume that the heart and other internal organs are equally prone to premature degenerative changes. The lesson to be learned is that when a patient with organic heart disease comes before us and there is no history of the more usual infections, syphilis should be suspected and confirmatory evidence diligently sought for, especially in patients at or after middle life. When the cardiac symptoms are not urgent it is advisable to prescribe a period of rest, together with a short mercurial course, before proceeding to the administration of the more direct cardiac remedies.

A CASE OF SYPHILITIC NEPHRITIS.—H. B. Day, Cairo, Egypt. *Lancet*, 1920, vol. cxcviii, p. 1009.

The immediate effect of salvarsan therapy on this patient was so striking that there can be little doubt that the nephritis was entirely syphilitic in origin. As in the majority of cases reported, nephritis appeared in the early secondary stage, about three months after infection. The author attributes the success of treatment (so far as it could be carried out) to the early use of adequate doses of the salvarsan compound instead of mercury. It seems improbable that a nephritis appearing during specific treatment of syphilis would respond so favorably as this case where no previous treatment had been received.

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Original Articles

ON THE REACTION OF PREGNANT AND LACTATING FEMALES TO INOCULATION WITH *TREPONEMA PALLIDUM*—A PRELIMINARY NOTE

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THE observation that a mother might give birth to a syphilitic child and suckle such a child without herself showing any obvious manifestation of syphilis formed the basis for what is known as Colles' law. By some, these circumstances were interpreted as indicating an immunity to infection on the part of the mother, but this view has been called in question and an alternative interpretation of the condition has been offered whereby the resistance of the mother would be explained upon the basis of an existing infection. This furnishes no explanation, however, for the absence of the usual manifestations of disease, if it be true that there is a certain class of women who may contract syphilis under the circumstances indicated without showing obvious signs of infection.

In some experiments carried out by us on rabbits, there was a suggestion that a clue to this anomalous situation might be obtained from a study of the reaction to infection exhibited by pregnant animals as contrasted with that of the normal. It is, of course, a well known fact that pregnant rabbits can be infected with *Treponema pallidum* and two of the most pronounced cases of generalized syphilis which have been reported were produced in this way. These animals were inoculated intravenously, however, with overwhelming doses of virus and such cases furnish little or no indication of the response which might be expected from local inoculations of the genitalia timed with reference to conception.

As an approach to this problem, two experiments were carried out with rabbits to determine the one fact of whether or not there was any difference in the reaction of the pregnant female and that of a normal animal, whether male or female, to an ordinary local inoculation of *Treponema pallidum*, and the way in which such a difference might be expressed.

EXPERIMENTAL

The procedure employed in these experiments was to mate normal females with males; 24 hours later, the females were inoculated on the ventral surface of the vulva near the junction of the mucous and cutaneous surfaces of the labia. The inoculations were made intradermally with 0.2 c.c. of a testicular emulsion containing an average of 1 to 3 spirochetes to the microscopic field. The animals were then separately caged and held for observation. The organism used was the Nichols strain of *Treponema pallidum*.

Without entering into all the aspects of the experiments, a brief report may be given of the local and something of the general reaction exhibited by these animals during the periods of pregnancy and early lactation.

RESULTS

The first experiment carried out was of a preliminary character designed chiefly to give orientation. Only four females were used in this experiment and one of them proved to be fourteen days pregnant at the time of inoculation.

Two animals of this group showed absolutely no reaction at the site of inoculation. One of them has been followed for four months

without the appearance of the slightest manifestation of infection either local or general. The second animal lived only 54 days after inoculation but during this time developed no local or general lesions.

The third animal of the series showed a slight infiltration along the margins of the labia which appeared between two and three weeks after inoculation. This was so slight that it would hardly have been noted had it not been known that the animal had been inoculated at this point. The infiltration disappeared completely before the birth of the young, but there was a slight recurrence which again disappeared within a short time. There was no glandular enlargement with this reaction and no other lesions have appeared during a period of more than four months' observation.

This animal gave evidence also of a constitutional disturbance in the development of emaciation and weakness. These conditions became apparent about the time the lesion appeared on the vulva and lasted for fully two months. Meantime, she gave birth to a litter of six young, one of which was born dead and four others died within a few days.

The fourth animal of the series proved to have been inoculated almost exactly at the middle of her pregnancy. There was no sign of a local reaction in this case until 54 days after inoculation or 37 days after the termination of pregnancy. The animal was then separated from her young and the lesion grew very rapidly forming a chancre of about 1 cm. in diameter.

The results obtained from these four animals were regarded as sufficiently suggestive to warrant further investigation and a second experiment was carried out in which the reaction of the pregnant animal was controlled by parallel inoculations of females in heat, normal females, and normal males inoculated on the foreskin by the same technic. There were four females mated and inoculated as in the previous experiment, two females in heat, three normal females, and three males all of which were inoculated with the same virus.

The results from the control animals may be stated very briefly. Within ten days after inoculation, the eight animals of this group all showed typical reactions at the site of inoculation together with a beginning lymphadenitis; in five of them the lesions developed very rapidly, but by the end of the third to the fourth week, all of them showed well-defined and actively growing lesions with a well-marked

lymphadenitis. The vulval lesion of one animal was a diffuse infiltration about the margins of the labia and did not grow to any considerable size, but the lesions of the other animals were circumscribed, indurated chancres which reached a centimeter or more in diameter.

The reaction of the four pregnant females during the first eight weeks was quite different from that of the controls. Two of them showed no sign of a syphilitic reaction at the site of inoculation and no alterations in the inguinal nodes. A third animal showed no reaction until a few days after the birth of the young when a slight infiltration developed at the point of inoculation and disappeared within seventy-two hours. The general condition of these three animals was unaffected.

The fourth animal of this group showed a tiny area of infiltration on the ventral surface of the vulva five days after inoculation; by the eighth day, there was a small indurated papule about 2 mm. in diameter and a slight enlargement and induration of the inguinal lymphnodes. These lesions persisted for about one week and then gradually diminished.

Meantime the animal showed a progressive weakness and emaciation; she eventually gave birth to a litter of nine young, one of which was born dead and the others lived for only a few hours. At this time, the vulval lesion was no more than a tiny copper-colored spot with no appreciable infiltration.

Four days later, a small papule appeared in the sulcus between the labia and grew to a size of about 4 mm., while the original lesion completely disappeared; there was no reaction in the lymphnodes, however, and the general condition of the animal remained unimproved at the end of the first eight weeks after inoculation.

Summarizing the immediate results of these experiments, it may be said that normal rabbits whether male or female, react to intradermal inoculations of the vulva or sheath by the prompt development of characteristic indurated lesions at the site of inoculation and a well marked lymphadenitis.

Of eight pregnant females inoculated in the same way, only four of them showed any clinical sign of infection whatsoever; in three of these, the reaction consisted of a very slight and transient infiltration at the site of inoculation, unaccompanied by lymphadenitis; one of these animals showed no constitutional disturbance, but the two in which the local reaction was most marked, showed profound constitu-

tional disturbances as well, each giving birth to a dead fetus, and of fifteen young born of these two females, only one survived beyond the first week of life.

The only inoculation of a pregnant animal which gave rise to a lesion comparable to those of the controls was made during the middle of pregnancy, but the lesion did not appear until towards the end of lactation.

It is too early to compare ultimate effects, but the indications are that the difference in the reaction of pregnant and of normal animals as determined by other standards is fully as great as that seen in the local reaction during the first few months following inoculation.

CONCLUSIONS

The results reported show very clearly that the reaction of the rabbit to a genital inoculation with *Treponema pallidum* which practically coincides with conception differs very decidedly from that of the normal animal inoculated in the same way and that this difference extends through the period of pregnancy and well into the period of lactation.

The differences noted are of two kinds: ordinarily, it appears that the defensive mechanism of the pregnant animal is capable of opposing a resistance to inoculations performed at the time of conception such that little or no clinical sign of infection appears—a condition possibly analogous to that upon which Colles' law was founded. In other instances, however, slight local lesions and marked constitutional disturbances are produced which suggest an ineffectual resistance to the infection or a breaking down of the defensive mechanism. From the occurrence of these two extremes, one would also expect to find a third type of condition approaching more nearly that seen in the normal animal.

The demonstration of these fundamental facts concerning the reaction of pregnant and lactating animals to inoculation with *Treponema pallidum* furnish a starting point for the investigation of a wide range of problems centering about the subjects of infection and resistance in states of pregnancy and lactation and, by contrast, may be the means of approach to the more general problem of the defensive mechanism of the normal animal.

A STANDARDIZED METHOD OF PERFORMING THE WASSERMANN REACTION

ADOPTED BY PUBLIC HEALTH, MUNICIPAL, AND HOSPITAL LABORATORIES
IN MASSACHUSETTS

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THE Bordet-Gengou phenomenon as applied by Wassermann, Nisser and Bruck in 1906 to the serodiagnosis of syphilis and as modified by many others since this time is now almost universally used. The numerous Wassermann methods have in general established the clinical specificity of complement inhibition by syphilitic serums and cerebrospinal fluids. Since the test is chiefly used by clinicians as an aid in the diagnosis and treatment of syphilis, there should be, as far as possible, a standard basis for interpretation. Nevertheless, very little progress has been made toward the choice of a uniform method of executing this important reaction. The following method is being published at this time because of its adoption by the large public health, municipal and hospital laboratories* in Massachusetts. It has served our purpose best because it is simpler than most methods, none of which has given consistently better results when simultaneously compared. It has been compared with the original Wassermann technic and with many of its

*At a meeting held in March, 1918, the following institutions were represented and adopted the method described: Massachusetts General Hospital, Boston; Dr. J. Homer Wright, Pathologist. Peter Bent Brigham Hospital, Boston; Dr. I. Chandler Walker, Associate in Med. Boston Board of Health; Dr. Philip Castleman, Bacteriologist. Sias Laboratory, Boston; Dr. Francis Slack, Director. Worcester Board of Health; James C. Coffey, Executive Officer. Brockton Board of Health; G. E. Bolling, City Bacteriologist and Chemist. Boston Laboratories (Private); L. W. Lee, Director. A Private Laboratory, Boston; A. R. G. Booth. Boston City Hospital, Boston; Dr. Frank B. Mallory, Pathologist. Westboro State Hospital, Westboro; Dr. Solomon C. Fuller, Pathologist. Base Hospital, Camp Devens; Dr. Leslie Spooner (in charge of Laboratory). Homeopathic Hospital, Boston; Dr. W. J. Watters, Pathologist. Boston Dispensary, Boston; Dr. Wm. A. Hinton, Pathologist.

modifications. During the past seven years extensive opportunity has been afforded to study its reliability. The material has been drawn chiefly from institutional cases where other laboratory tests and where the clinical facilities for diagnosing syphilis have been unusually good.

GLASSWARE AND APPARATUS

Before considering the preparation of reagents and the technic of their titration, it is well to describe briefly such apparatus as contributes to the accuracy of the method.

All glassware should be of good quality and sufficiently thick to prevent easy breaking. Jena glass and other expensive kinds add nothing to the accuracy of the method.

Test tubes 120 mm. long, 18 mm. in diameter, and 1 mm. thick are suitable for the titrations and the tests. Test tubes 100 mm. long, 12 mm. in diameter, and 1 mm. thick, are especially convenient for serums. For the preparation of reagents, wide-mouth, thick, clear, colorless, glass bottles with a large base, and of 200 to 500 c.c. capacity are especially adapted. Pipettes which have thick tips should be selected so that they will not break easily when the tips strike the bottom of the reagent bottles. Convenient sizes of pipettes are 0.5 c.c., 1.0 c.c., 2.0 c.c., 5.0 c.c. and 10 c.c. each graduated in tenths of a cubic centimeter. It is best that the graduation should extend no lower than 1 cm. from the tip and that the graduated portion of each pipette measure no less than 20 cm. long.

All new glassware should be boiled in dilute nitric acid (2.0 c.c. concentrated nitric acid to one liter of tap water) and then thoroughly washed in cold running tap water until every trace of acid has been removed. Glassware used in the test and titrations should be thoroughly cleansed as soon after use as possible with cold running tap water, so as to remove protein material, and then dried in a hot air oven. From time to time glassware should be placed in a cleaning solution consisting of two parts of potassium bichromate, three parts of crude sulphuric acid, and twenty-five parts of water, where it should remain for twelve hours or more and then be rinsed in hot running tap water until all traces of acid are removed. Frequent cleaning in this way will prevent the accumulation of proteins upon the surface of the glassware. In general, it may be said

that all glassware should be chemically clean. It is not always necessary, however, to sterilize it except when specified in the technic of the method.

Heavy brass wire test tube racks holding 40 tubes (being four tubes wide and ten tubes long) are convenient for the tests and titrations. The space for each tube should be about $\frac{3}{4}$ inch square. These racks should be partitioned about one inch from the bottom, as well as on the top, so that the tubes will not be displaced by handling and shaking. Test tube racks of similar construction and material (except that the partitions should be about $\frac{1}{2}$ inch square) are used to hold the serums during inactivation and subsequent manipulations. These racks, however, should have sufficient capacity for the maximum number of specimens to be tested at one time. Further, it is best that these racks hold ten tubes or some multiple of ten. This will avoid errors and confusion when the serums are being pipetted for the Wassermann reaction.

For the purpose of incubation it is essential to employ a water-bath containing enough water to prevent appreciable lowering of temperature when 300 to 500 tubes are immersed. Incubation temperature should not vary more than one degree centigrade from 37° C. For inactivation a water-bath should be used which maintains a temperature of from 55° to 56° C. Higher temperatures than 56° C., even if maintained for only a short time, are very detrimental.

PREPARATION OF REAGENTS

Antigen.—This reagent is prepared from fresh human heart muscle (less than twenty-four hours postmortem, if possible). The connective tissue and fat are removed from the heart with scissors. The heart muscle is then cut into pieces of about 1 c.c., weighed, and the weight recorded. These pieces are kept for one or two weeks in a tightly covered mason jar containing sufficient 95 per cent alcohol to cover them. The hardened pieces of heart tissue are then removed from the alcohol and ground as finely as possible with an ordinary meat grinder. The alcohol used to harden the pieces of heart muscle and an additional quantity of 95 per cent alcohol should be added to the ground heart tissue to make the proportion of heart weight to total alcoholic volume equal 1:10; that is, 100 grams of heart tissue will require a total of 1000 c.c. of 95

per cent alcohol. This alcoholic suspension of ground heart tissue is allowed to stand in the incubator at 37° C. for from two to three weeks. Daily shaking by hand is required. About 100 c.c. of the alcoholic extract, free from heart fragments and sediment, is decanted and saturated with cholesterin. This saturation can be done most easily by adding about 0.7 gm. of cholesterin to 100 c.c. of the alcoholic extract and incubating at 37° C. for from twelve to eighteen hours. The cholesterinized heart extract is then allowed to stand at 20° C. in a water-bath for five or six hours. If cholesterin crystallizes out, the extract is saturated; otherwise, the procedure is repeated until saturation occurs. After saturation, the excess of cholesterin should be removed by filtering through ordinary filter paper. To the clear filtrate an equal amount of the filtered uncholesterinized alcoholic extract of heart muscle should be added. This makes the *stock antigen*. It will keep indefinitely at room temperature, but should not be kept in the refrigerator because most of the cholesterin will recrystallize. For routine tests, the stock antigen is freshly diluted with physiologic salt solution. (See Procedure under Table IV.)

Complement.—This is obtained from guinea pig's blood. From 8 c.c. to 15 c.c. of blood may be secured by cutting the carotid artery or preferably, by aspirating 6.0 c.c. to 10 c.c. of blood from the heart of a full grown guinea pig. An 18 or 19 gauge needle attached to a 10 c.c. Luer syringe may be used for this operation which most of the guinea pigs survive. If the guinea pigs are bled from the heart, the interval of bleeding should not be less than three weeks. No less than three guinea pigs should be bled for making any test or titration and the blood obtained pooled (mixed). The pooled blood is allowed to stand for one to two hours at 37° C. to hasten the separation of the serum. The serum is then withdrawn and centrifuged to remove the corpuscles. The clear serum, which contains complement, is diluted with physiologic salt solution to make a 10 per cent solution; that is, one part of guinea pig's serum plus nine parts of physiologic salt solution. The guinea pig's serum, diluted, (complement) should be kept in a refrigerator to keep it cool and to prevent exposure to intense sunlight because heat and sunlight effect its strength. Experience has shown that complement prepared and used on the same day gives the most dependable results.

Guinea pigs which are fed on any mixed ration consisting largely of carrots appear to yield the most uniform complement.

Washed Sheep's Corpuscles.—These are prepared from freshly obtained, defibrinated blood. The blood may be obtained by thrusting a 12 gauge needle or trochar into the external jugular vein of a sheep and allowing from 25 c.c. to 100 c.c. of blood (as required) flow into a thick glass bottle containing glass beads. A rubber tourniquet should be placed around the sheep's neck before the puncture to make the blood flow more rapidly. If a sheep is not kept for this purpose, blood may be obtained from a local abattoir. The blood must be constantly shaken for at least five minutes to prevent clotting. It is then strained through thin sterile gauze into 50 c.c. or 100 c.c. centrifuge tubes. In order to remove the serum four or five volumes of physiologic salt solution are added to the blood in the centrifuge tubes. These are centrifuged and as much of the supernatant fluid as possible is poured off. The corpuscles are washed three times in this way. Finally enough physiologic salt solution is added to make the volume of washed cells equal to that of the defibrinated blood originally used. This suspension of corpuscles in salt solution is called washed sheep's corpuscles and will keep for from three to five days in the refrigerator. The suspension is unsuitable for use when it shows spontaneous hemolysis. A standardized 5 per cent suspension of washed sheep's corpuscles—called standardized cells—is used in the test and titrations.

Standardized Cells.—A 5 per cent suspension of washed sheep's corpuscles is not always uniform because a greater or lesser clot may be formed during the process of defibrinating the sheep's blood. In order to employ a suspension of uniform strength it is necessary to have a standard for comparison. A color standard may be made by adding red ink and a small amount of methylene blue to 0.5 per cent carbolized tap water. This colored mixture is so adjusted as to give a concentration of color equivalent to 0.5 c.c. of a carefully* and accurately prepared suspension of washed sheep's corpuscles, which have been hemolyzed by the addition of 1.5 c.c. of tap water. After this color standard has been properly adjusted it will keep indefinitely. Each new suspension of cells should be standardized. Two small homeopathic vials of about the same diameter as the tubes employed in the test and titrations are

*This applies particularly to the prevention of partial clotting during the process of defibrinating the blood.

suitable for the comparison. In order to do this 5.0 c.c. of washed sheep's corpuscles are added to 95 c.c. of physiologic salt solution. Five-tenths of a cubic centimeter of this suspension is accurately pipetted into one of the vials, 1.5 c.c. of tap water is added and the vial shaken by hand until the cells are hemolyzed. This solution of hemolyzed cells is then compared with 2 c.c. of the color standard. If the intensity of color is not the same as that of the standard, the suspension should be adjusted to make it so. A suspension prepared in this way is called *standardized cells*. In practice it is often necessary to use 6 c.c. or 7 c.c. washed sheep's corpuscles with 95 c.c. of physiologic salt solution.

Amboceptor.—Amboceptor is obtained from rabbit's blood and is prepared by injecting washed sheep's corpuscles into the peritoneal cavity of a full grown rabbit at three or four day intervals. Freshly obtained and prepared washed sheep's corpuscles must be used for each injection. The amount of the first injection is about 7.0 c.c., the second 14 c.c., the third 21 c.c., and the fourth about 28 c.c. On the eighth or ninth day after the last injection the rabbit is bled from the ear, after moistening its surface with xylol, to obtain from 2 to 3 c.c. of blood. This blood is allowed to clot, and clear serum is removed and heated in a water-bath at 55° C. for one-half hour, in accordance with the preparation of stock amboceptor (q. v.). This heated immune rabbit's serum (*amboceptor*) is titrated immediately according to Table I, to see whether it is sufficiently strong to be used in the Wassermann reaction. It is inconvenient to use an amboceptor with a titre less than 1:1000. If the amboceptor is strong enough for convenient use, 40 to 60 c.c. of blood is obtained from the rabbit's heart and delivered in a sterile, covered bottle. For bleeding, a large syringe and an 18 or 19 gauge needle should be used. On the other hand, should the titre be less than 1:1000, a fifth intraperitoneal injection of 35 c.c. of washed sheep's corpuscles is immediately made. After a period of five days from the fifth injection 40 to 60 c.c. is obtained from the heart and treated as described below. After an intervening rest of from four to six weeks and upon being reimmunized, the same rabbit may be used repeatedly for the production of amboceptor.

Stock amboceptor is prepared from the immune rabbit's blood according to the following method: place the bottle containing the 40 c.c. to 60 c.c. of immune rabbit's blood in a water-bath at 37° C.

for from one-half to three-quarters of an hour to hasten the separation of the serum. All of the serum is withdrawn with a pipette and delivered into a sterile 100 c.c. centrifuge tube and stoppered with a sterile cork. It is then centrifuged to remove the corpuscles and distributed in 2 c.c. to 5 c.c. quantities into small sterile test tubes. The tubes containing the serum are heated to 55° C. for one-half hour and corked with sterile paraffined stoppers. This heating is done to prevent bacterial growth. Each of the tubes contains *stock amboceptor* which should be titrated, according to Table I, before it is used. Stock amboceptor keeps indefinitely in a refrigerator. Bacterial contamination may effect its role in hemolysis but rarely does.

Sensitized Cells.—These are prepared by mixing equal parts of standardized cells and dilute amboceptor. (See discussion under Table I.) This mixture is incubated in a water-bath at 37° C. for one-half hour to sensitize the cells. One cubic centimeter of a freshly prepared mixture is used in the Wassermann reaction.

Physiologic Salt Solution.—This is prepared by adding 8.5 grams of sodium chloride (c.p.) to 1000 c.c. of distilled water. It is better (but not absolutely necessary) to sterilize it by boiling or autoclaving.

PREPARATIONS OF SERUMS AND SPINAL FLUIDS FOR TESTING

The blood is preferably withdrawn from the patient with a Luer syringe, immediately delivered into a test tube, and allowed to stand at room temperature until it clots. After the blood has clotted it should be gently shaken to loosen the clot from the sides of the tube, and then placed in a refrigerator. The serum should be poured, not later than the third day, into a small test tube and inactivated at 55° C. for one-half hour. This is chiefly to destroy the complement, but it also inhibits bacterial growth. If the serum is not clear because of the presence of corpuscles, it should be centrifuged, and the clear serum poured off for inactivation. If the amount of serum is small, it is better to withdraw it with a medicine dropper which has a long tip. Only one such dropper is necessary, provided it is very carefully washed with salt solution at least three times before using it for another serum. If the serum is not tested for two or more days after inactivation, it should be preserved by the addition of 5 per cent carbolic acid in physiologic salt solution

in the proportion of ten parts of serum to one part of the carbolic acid solution. If one wishes to test the specimen the day it is obtained from the patient, it should be placed in a water-bath at 37° C. for one-half to three-quarters of an hour to hasten the separation of the serum, centrifuged, and the serum withdrawn and inactivated.

Although the preparation of serums is very simple in practice, experience is necessary to develop technic which will give reliable results. A large proportion of anticomplementary serums usually indicates that they are improperly prepared.

Spinal fluids are not inactivated before testing. If they are to be kept for several days, they should be preserved by the addition of 5 per cent carbolic acid solution in the proportion of ten parts of the spinal fluid to one part of the carbolic acid solution and kept in the refrigerator.

TITRATION OF REAGENTS AND THE WASSERMANN REACTION

After the reagents have been prepared, it is necessary to determine their quantitative relationships by titration. The following outline gives the steps in this procedure:

1. The amboceptor should be titrated according to Table I.
2. The test for anticomplementary and natural hemolytic properties should be made according to Table III. As a preliminary procedure for this titration "the complement titre" should be obtained according to Table II (Rows I and V only are used in this preliminary titration).
3. The Wassermann reaction should be performed according to Table IV after having performed the entire titration according to Table II as a preliminary step.

In the tables which follow, each square represents a space in the rack containing a test tube into which the reagents are pipetted according to directions.

PROCEDURE

I. Prepare:

1. Cells—a standardized 5 per cent suspension of washed sheep's corpuscles in physiologic salt solution.
2. Complement—a 10 per cent solution of guinea pig's serum in physiologic salt solution.
3. Amboceptor.—This is prepared from (stock amboceptor) by diluting with physiologic salt solution in the following manner: Pipette very ac-

TABLE I
TITRATION OF AMBOCEPTOR

Row I To show that each reagent has no hemolyzing effect; therefore, no tube in this row should show hemolysis.	Amboceptor	(1:500)						
	Complement	0.5 c.c.	0.5 c.c.						
	Cells	0.5 c.c.	0.5 c.c.	0.5 c.c.						
	Salt									
	Solution	1.5 c.c.	1.5 c.c.	2.0 c.c.						
Row II To determine the unit of amboceptor.	Amboceptor	(1:500)	(1:1000)	(1:1500)	(1:2000)	(1:2500)	(1:3000)	(1:3500)	(1:4000)	(1:4500)
	Complement	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.
	Cells	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.
	Salt	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.
	Solution	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.

DIAGRAM OF DILUTIONS OF AMBOCEPTOR

Amboceptor diluted 1:100	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.
Physiologic salt solution	0.4 c.c.	0.9 c.c.	1.4 c.c.	1.9 c.c.	2.4 c.c.	2.9 c.c.	3.4 c.c.	3.9 c.c.	4.4 c.c.	4.9 c.c.	
Resulting dilution of amboceptor	1:500	1:1000	1:1500	1:2000	1:2500	1:3000	1:3500	1:4000	1:4500	1:5000	

curately 0.1 c.c. of the stock amboceptor (see page 7) into a test tube, and add 9.9 c.c. of 0.85 per cent salt solution. This makes a dilution of 1:100. From the dilution of 1:100 the following dilutions are prepared according to the diagram below. A separate test tube and a separate pipette should be used for the preparation of each dilution and each should be vigorously shaken before pipetting. (See Diagram, p. 606.)

II. Pipette in the following order according to Table I:

1. Amboceptor with a 1.0 c.c. pipette,
2. Complement with a 5.0 c.c. pipette,
3. Cells with a 5.0 c.c. pipette, and,
4. Salt solution with a 10 c.c. pipette.

A separate pipette should be used for each reagent and it should be placed in a flat pan half full of cool tap water after use. This applies to every pipetting procedure.

III. Incubate in water-bath one hour at 37C.

IV. Read the results of the titration.

- V. Make a final titration by employing amboceptor dilutions which differ by 100 between the limits of complete and partial hemolysis. Suppose the tubes containing a dilution of 1:1000 shows complete hemolysis and the tube which contains the 1:1500 dilution shows partial hemolysis; then a final titration should be made by employing amboceptor dilutions of 1:1000, 1:1100, 1:1200, 1:1300, 1:1400 and 1:1500. The technic is otherwise a repetition of the above procedure. When the preliminary titre is above 1:4000 it is better to dilute two to three cubic centimeters of the stock amboceptor so that its strength will be about 1:2000, and then make a final titration as above directed. Amboceptor so diluted gradually loses its potency and therefore, should be carefully watched to discover any slight change in its hemolyzing power.

DISCUSSION

The largest dilution showing complete hemolysis contains the unit. The unit of amboceptor, therefore, may be defined as the quantity of heated immune rabbit's serum which hemolyzes 0.5 c.c. of a standardized 5 per cent suspension of washed sheep's corpuscles in the presence of 0.5 c.c. of 10 per cent guinea pig serum (complement). Two units of amboceptor are used in the other titrations and in the Wassermann reaction. For convenience, the rabbit's immune serum is diluted with physiologic salt solution so that 0.5 c.c. contains two units. The method of making such a dilution is shown in the following illustration: Suppose that the tubes containing dilutions greater than 1:1200 show gradually increasing inhibition of hemolysis, the amboceptor should be used in a dilution of 1:600 which is prepared by very accurately pipetting 0.1 c.c. of the stock amboceptor into a flask or bottle of 100 to 300 c.c. capacity and adding 60 c.c. of physiologic salt solution and then thoroughly shaking. This latter solution is called *dilute amboceptor*, 0.5 c.c. of which is used in the test and in the subsequent titrations. Dilute amboceptor may weaken in two to four days after its preparation even if kept in the refrigerator.

TABLE II
COMBINED TITRATION OF COMPLEMENT, AMBOCEPTOR AND ANTIGEN

Row I To show that each reagent has no hemolyzing effect. Therefore, no tube in this row should show hemolysis.	Complement	1.0 c.c.								
	Amboceptor	0.5 c.c.								
	Cells	0.5 c.c.								
	Salt Solution	1.0 c.c.	1.5 c.c.	2.0 c.c.								
Row II To show that <i>dilute antigen C</i> has been properly prepared. Then it has little or no anticomplementary effect.	Complement	0.5 c.c.	0.4 c.c.	0.3 c.c.	0.2 c.c.	0.1 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.
	Amboceptor	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.4 c.c.	0.4 c.c.	0.3 c.c.	0.2 c.c.	0.2 c.c.	0.1 c.c.
	Cells	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.
	Antigen C	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.
	Salt Solution	0.5 c.c.	0.6 c.c.	0.7 c.c.	0.8 c.c.	0.9 c.c.	0.9 c.c.	0.1 c.c.	0.2 c.c.	0.3 c.c.	0.3 c.c.	0.4 c.c.
Row III To show that <i>dilute antigen B</i> has been properly prepared. Then it has little or no anticomplementary effect.	Complement	0.5 c.c.	0.4 c.c.	0.3 c.c.	0.2 c.c.	0.1 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.
	Amboceptor	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.4 c.c.	0.4 c.c.	0.3 c.c.	0.2 c.c.	0.2 c.c.	0.1 c.c.
	Cells	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.
	Antigen B	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.
	Salt Solution	0.5 c.c.	0.6 c.c.	0.7 c.c.	0.8 c.c.	0.9 c.c.	0.9 c.c.	0.1 c.c.	0.2 c.c.	0.3 c.c.	0.3 c.c.	0.4 c.c.
Row IV To show that <i>dilute antigen A</i> has been properly prepared. Then it has little or no anticomplementary effect.	Complement	0.5 c.c.	0.4 c.c.	0.3 c.c.	0.2 c.c.	0.1 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.
	Amboceptor	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.4 c.c.	0.3 c.c.	0.2 c.c.	0.2 c.c.	0.1 c.c.
	Cells	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.
	Antigen A	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.
	Salt Solution	0.5 c.c.	0.6 c.c.	0.7 c.c.	0.8 c.c.	0.9 c.c.	0.9 c.c.	0.1 c.c.	0.2 c.c.	0.3 c.c.	0.3 c.c.	0.4 c.c.
Row V To determine the unit of complement.	Complement	0.5 c.c.	0.4 c.c.	0.3 c.c.	0.2 c.c.	0.1 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.
	Amboceptor	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.4 c.c.	0.4 c.c.	0.3 c.c.	0.2 c.c.	0.2 c.c.	0.1 c.c.
	Cells	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.
	Salt Solution	1.0 c.c.	1.1 c.c.	1.2 c.c.	1.3 c.c.	1.4 c.c.	1.4 c.c.	0.6 c.c.	0.7 c.c.	0.8 c.c.	0.8 c.c.	0.9 c.c.

PROCEDURE

I. Prepare:

1. Cells.—A standardized 5 per cent suspension of washed sheep's corpuscles in physiologic salt solution.
2. Complement.—A 5 per cent solution made by diluting 12 c.c. of the 10 per cent guinea pig's serum with 12 c.c. of physiologic salt solution.
3. Dilute Amboceptor.—Diluted stock amboceptor, 0.5 c.c. of which contains two units.
4. Dilute antigen.—For technic of its preparation (see Procedure I under Table IV).

II. Pipette in the order indicated in Table II:

1. Five per cent complement with a 2 c.c. pipette,
2. Dilute amboceptor with a 5 c.c. pipette,
3. Dilute antigen with a 5 c.c. pipette,
4. Cells with a 5.0 c.c. pipette and,
5. Physiologic salt solution with a 10 c.c. pipette.

III. Incubate in water-bath for one-half hour at 37°C.

IV. Read the results of the titration.

DISCUSSION

This titration is always made immediately before testing specimens by the Wassermann reaction (Table IV).

The tube in Row V containing the smallest amount of complement that causes complete hemolysis contains the unit. Two units or an equal amount of 10 per cent complement is used in the test. For example—suppose 0.4 c.c. is the smallest amount of the 5 per cent guinea pig serum that gives complete hemolysis, then 0.4 c.c. of the 10 per cent solution should be used in the test.

For convenience the 10 per cent guinea pig serum is diluted with salt solution so that 0.5 c.c. contains two units of complement. Such a solution is called *dilute complement*. In this example where the complement titre is 0.4 c.c. the 10 per cent guinea pig serum is again diluted by the addition of one part of physiologic salt solution to each four parts of the 10 per cent guinea pig serum to make it have the concentration of *dilute complement*. The hemolytic system is suitably adjusted for the Wassermann reaction when the tube in Row V containing 0.3 c.c. of amboceptor is completely hemolyzed and the one containing 0.2 c.c. is moderately hemolyzed. With correct technic the degree of hemolysis will be proportional to the amount of complement in the first five tubes of each row. Guinea pig serum which gives a complement titre of less than 0.3 c.c. or greater than 0.5 c.c. usually does not give dependable results.

PROCEDURE

I. Prepare:

1. Cells.—A standardized 5 per cent suspension of washed sheep's corpuscles in physiologic salt solution.
2. Dilute complement.—10 per cent guinea pig serum diluted so that 0.5 c.c. contains 2 units. Before setting up this titration, determine the complement unit according to Table II, using Rows I and V only.

TABLE III
TITRATION FOR THE NATURAL HEMOLYTIC AND ANTICOMPLEMENTARY PROPERTIES OF ANTIGEN

Row I To determine the natural hemolytic properties of antigen. Usually no tube in this row shows hemolysis.	Antigen Complement Cells Salt Solution	1.0 c.c.	0.8 c.c.	0.6 c.c.	0.4 c.c.	0.2 c.c.	0.1 c.c.	0.05 c.c.
		0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.
		0.5 c.c.	0.5 c.c.	0.5 c.c.	1.1 c.c.	1.3 c.c.	1.4 c.c.	1.45 c.c.
Row II To determine the largest amount of antigen that does not inhibit hemolysis. Usually tubes containing 0.4 c.c. or more antigen show inhibition of hemolysis.	Antigen Complement Salt Solution	1.0 c.c.	0.8 c.c.	0.6 c.c.	0.4 c.c.	0.2 c.c.	0.1 c.c.	0.05 c.c.
		0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.
		0.2 c.c.	0.4 c.c.	0.6 c.c.	0.8 c.c.	0.9 c.c.	0.95 c.c.
Row III To show the amount of turbidity due to cholesterolin and other lipoidal substances contained in antigen.	Antigen Hemolyzed cells Salt Solution	1.0 c.c.	0.8 c.c.	0.6 c.c.	0.4 c.c.	0.2 c.c.	0.1 c.c.	0.05 c.c.
		1.5 c.c.	1.5 c.c.	1.5 c.c.	1.5 c.c.	1.5 c.c.	1.5 c.c.	1.5 c.c.
		0.2 c.c.	0.4 c.c.	0.6 c.c.	0.8 c.c.	0.9 c.c.	0.95 c.c.

3. Dilute amboceptor—diluted stock amboceptor, 0.5 c.c. of which contains 2 units. (See discussion under Table I.)
4. Antigen—a dilution of the stock antigen prepared by taking 3.0 c.c. of stock antigen and adding 12.00 c.c. of physiologic salt solution drop by drop and shaking well after the addition of each drop.
5. Sensitized cells—a mixture consisting of 5.0 c.c. of a standardized suspension of washed sheep's corpuscles and 5.0 c.c. of dilute amboceptor.
6. Hemolyzed cells.—These are prepared by adding 10.0 c.c. of tap water to 5.0 c.c. of the standardized 5 per cent suspension of washed sheep's corpuscles and shaking until the cells are hemolyzed.

II. Pipette:

1. Antigen—(diluted one plus four as above described) with a 2 c.c. pipette.
2. Complement with a 5 c.c. pipette,
3. Standardized cells with a 5 c.c. pipette in Row I,
4. Hemolyzed cells with a 10 c.c. pipette in Row III, and,
5. Physiologic salt solution with a 10 c.c. pipette.

III. Incubate in water-bath at 37°C. for 40 minutes.

IV. Pipette 1.0 c.c. of sensitized cells with a 10 c.c. pipette, into each tube in Row II.

V. Incubate one hour longer.

VI. Read results of titration.

DISCUSSION

Cholesterinized antigens cause a turbidity proportional to the amount of antigen. This turbidity should not be mistaken for the inhibitory effect of the antigen upon the complement. Compare Rows II and III in order to determine the strictly anticomplementary effect of the antigen.

An available antigen contains no natural hemolytic properties either in one-half the amount or in twice the amount to be employed in the test, while the degree of anticomplementary effect is variable. A maximum of one-half the largest amount causing no inhibition may be used in testing unknown serums and spinal fluids.

The only way to standardize an antigen either qualitatively or quantitatively is by testing its inhibitory properties against a large number of known positive and negative specimens of blood and spinal fluid.

PROCEDURE

- I. Prepare enough of the following reagents to perform the necessary titrations and tests for the entire day.
 1. Cells—a standardized 5 per cent suspension of washed sheep's corpuscles in physiologic salt solution.
 2. Dilute complement—10 per cent guinea pig serum titrated according to Table II, and diluted with physiologic salt solution so that 0.5 c.c. contains two units.
 3. Dilute amboceptor—diluted stock amboceptor 0.5 c.c. of which contains two units.

TABLE IV
THE WASSEMANN REACTION

	REAGENTS	EACH SERUM FOR WASSEMANN TEST					ANTIGEN CONTROLS	To show that twice the amount of antigen used in the reaction is not anticomplementary. Therefore, hemolysis should be complete in each tube.
		POSITIVE CONTROL	DOUBTFUL CONTROL	SERUM FOR CONTROL	NEGATIVE CONTROL	SERUM FOR CONTROL		
Row I	Serum	0.2 c.c.	0.2 c.c.	0.2 c.c.	0.2 c.c.	0.2 c.c.	1.0 c.c.	
Serum Controls*	Comp-sal-mixt.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	
Row II	Serum	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.5 c.c.	Dilute Antigen C. 0.5 c.c.
Tests with Antigen C.	Comp-sal-ant. C. mixt.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.
Row III	Serum	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.5 c.c.	Dilute Antigen B. 0.5 c.c.
Tests with Antigen B.	Comp-sal-ant. B. mixt.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.
Row IV	Serum	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.1 c.c.	0.5 c.c.	Dilute Antigen A. 0.5 c.c.
Tests with Antigen A.	Comp-sal-ant. A. mixt.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.	1.0 c.c.

*To show that twice the amount of each serum or spinal fluid used in the Wassermann reaction is not anticomplementary, therefore, hemolysis should be complete for each specimen that gives a satisfactory test.

4. Dilute antigen.—Calculate the amount of stock antigen required for the day's test and for the combined titration of complement, amboceptor and antigen (see Table II). Pipette this amount of stock antigen into a glass bottle or flask, add the four parts of physiologic salt solution drop by drop (shaking well after the addition of each drop) and again dilute with physiologic salt solution so that each 0.5 c.c. of the resulting mixture contains the amount of antigen used in the Wassermann reaction. Dilute antigen should be freshly prepared for each day's test.
5. Complement-saline-antigen-mixture.—This is prepared as follows: Mix enough of the dilute antigen A with an equal amount of dilute complement to perform the day's test. In like manner make complement-saline-antigen-mixture for antigens B and C.

CALCULATIONS FOR THE PREPARATION OF COMPLEMENT-SALINE-ANTIGEN-MIXTURE

FOR 35 SPECIMENS

Tubes to contain antigen A:	50 x 0.15 antigen A.....	7.5 c.c.
1. for titration of Table II..	9 tubes	50 x 0.35 salt solution.....
2. for 35 specimens	35 tubes	17.5 c.c.
3. for working margin.....	6 tubes	Total amt. dilute antigen A..
		25.0 c.c.

Total number required.....50 tubes

In this example it is assumed that experience has shown that 0.15 c.c. of the one plus four dilution of this particular stock antigen A contains the correct amount of inhibitory property for one specimen. To make 7.5 c.c. of this one plus four antigen as needed for the 50 tubes, take 1.5 c.c. of stock antigen A and add 6.0 c.c. of physiologic salt solution drop by drop as previously directed.

Likewise it has been found that 0.1 c.c. of this particular antigen B and 0.075 c.c. of this particular antigen C. (the one plus four dilutions) contain the proper amount of antigenic property. The calculations which follow for the preparation of the antigens are otherwise similar.

50 x 0.1 antigen B.....	5.0 c.c.	50 x 0.075 antigen C.....	3.75 c.c.
50 x 0.4 salt solution.....	20.0 c.c.	50 x 0.425 salt solution.....	21.25 c.c.

Total amount of dilute
antigen B..... 25.0 c.c.

Total amount dilute
antigen C.....25.00 c.c.

To calculate the number of tubes to contain dilute complement, multiply the number of tubes (50 in this example) by four so that there will be enough for each of the three antigens and for the serum controls. (See Table IV.) Then multiply this number (200) by the complement titre 0.4 since it is assumed that four-tenths of a cubic centimeter of this particular complement contains two units as determined by titration according to Table II.

200 x 0.4 complement.....	80.00 c.c.
200 x 0.1 salt solution	20.00 c.c.

Total amt. dilute complement..100.00 c.c.

Mix 25 c.c. of the dilute antigen A with 25 c.c. of dilute complement. This makes 50 c.c. of complement-saline-antigen mixture (abbreviated: comp-sal-ant.

mix.) which is enough for the day's test. Likewise prepare complement-saline-antigen mixtures from stock antigen B and C. The remaining 25 c.c. of dilute complement is for use in Row I.

6. Complement-saline-mixture—equal parts of dilute complement and physiologic salt solution.
7. Sensitized cells—equal parts of standardized 5 per cent suspension of washed sheep's corpuscles and dilute amboceptor which have been incubated together for one-half hour at 37°C.

II. Pipette:

1. The serums with a 0.5 c.c. pipette and spinal fluids with a 1.0 c.c. pipette graduated in tenths in the amounts indicated in the table. Use a separate pipette for each specimen. In practice it is often necessary to use half quantities spinal fluid and of each reagent in testing it because the amount of spinal fluid submitted for examination will not admit of the full amounts as indicated in the table. Important: Carefully inspect each tube to be certain that it contains the proper serum or spinal fluid. This may be done by matching the color of each specimen in the test with that of the serum or spinal fluid in the inactivating rack.
 2. Five tenths of a cubic centimeter of the dilute antigen A with a 10 c.c. pipette into the antigen control tube Row IV.
 3. Five tenths of a cubic centimeter of dilute antigen B with a 10 c.c. pipette into the antigen control tube, in Row III.
 4. Five tenths of a cubic centimeter of dilute antigen C with a 10 c.c. pipette into the antigen control tube, Row II.
 5. One cubic centimeter of the complement-saline-antigen mixture (prepared from the stock antigen A) with a 10 c.c. pipette into each of the tubes in Row IV.
 6. One cubic centimeter of the complement-saline-antigen mixture (prepared from stock antigen B) with a 10 c.c. pipette into each of the tubes in Row III.
 7. One cubic centimeter of the complement-saline-antigen mixture (prepared from stock antigen C) with a 10 c.c. pipette into each of the tubes in Row II.
 8. One cubic centimeter of complement-saline mixture with a 10 c.c. pipette into each tube in Row I.
- III. Shake each rack containing the tubes so that the contents will be thoroughly mixed.
- IV. Incubate at 37°C. for forty minutes.
- V. Pipette 1.0 c.c. of sensitized cells with a 10 c.c. pipette into each tube.
- VI. Shake the racks again to mix contents in tubes.
- VII. Incubate at 37°C. for one hour.
- VIII. Read the results. Complete or moderate inhibition of hemolysis with antigen A, B, and C, equals positive. Slight inhibition of hemolysis (75 per cent or more the cells hemolyzed) with antigen A and B, together with slight or no hemolysis with antigen C equals doubtful. Complete hemolysis with all antigens equals negative.

DISCUSSION

Antigen A and Antigen B should be prepared according to direction given on page 600. Each is obtained from a different human heart. Each should inhibit to the same degree in the presence of 0.1 c.c. of any positive serum or 0.5 c.c. of any positive spinal fluid. It is not necessary that the fixing amounts be equal, for example in the above illustration, 0.15 c.c. of antigen A, has the same fixing power as 0.1 c.c. of antigen B. It is essential to use two antigens in this way because faulty technic in preparing the dilutions of the antigens or in pipetting the serums or spinal fluids are easily detected by this comparison.

Antigen C is prepared from guinea pigs' hearts which have been allowed to stand in 95 per cent alcohol for two months or more, otherwise the method of preparation is the same as for the human heart antigen. Antigen C as employed in the State Wassermann Laboratory is more sensitive than either antigens A or B, and is therefore, useful in selecting the presumptive positives from the negatives. As a preliminary test, each specimen is prepared and set up according to Row II only (no serum control is necessary for this preliminary test). Since antigen C is more sensitive than the other two antigens, those specimens which show inhibition of hemolysis are presumptively positive. Such specimens are selected, placed in a separate rack, and in the afternoon are not only re-tested with antigen C, but also tested with antigens A and B, the whole test being exactly as indicated in Table IV. Complement prepared from the same guinea pigs' serum is used in the preliminary test and in the Wassermann reaction as given in Table IV.

CONCLUSION

The reaction as carried out by this method is reported and interpreted as follows: POSITIVE indicates syphilis, except very rarely in acute febrile conditions such as malaria and pneumonia. NEGATIVE does not exclude syphilis. In dealing with obscure conditions, less than three negatives has little diagnostic significance. DOUBTFUL suggests syphilis. It is, therefore, advisable to have three or more specimens submitted in such a case. A persistently or predominately doubtful reaction usually indicates syphilis. UNSATISFACTORY means that the test was unsuccessful either because of the condition of the specimen or because of some difficulty with technic.†

*Standardized antigens and standardized amboceptor are furnished to any laboratory in Massachusetts to perform the Wassermann test according to this method.

†Hemolyzed specimens of blood, bacterially or chemically contaminated specimens frequently give unreliable results even if they are not anticomplementary. The presence of bacterial or chemical contamination is usually indicated by a purplish, brownish or other unusual discoloration of the mixture after the test has been incubated for the last time.

STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. XII

THE TITRATION OF HEMOLYSIN AND SENSITIZED VERSUS PLAIN RED BLOOD CORPUSCLES IN COMPLEMENT-FIXATION TESTS*

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IN THE technic of complement-fixation tests it is the usual custom to add hemolysin and cells separately after the primary incubation; in some laboratories, however, the hemolysin and cells are mixed and allowed to stand at varying temperatures for varying periods of time and the "sensitized" corpuscles added. This practice is particularly in vogue with the antisheep and antiox hemolytic systems, but not with the antihuman, because the presence of hemagglutinins in rabbit antihuman serum generally interferes with sensitization and the use of sensitized corpuscles.

The use of sensitized corpuscles decreases somewhat the amount of work connected with the conduct of complement-fixation tests and generally yields more rapid and sharper hemolysis, as compared with the usual method of adding corpuscles and hemolysin separately; but of greater importance is the effect produced upon the sensitiveness and accuracy of the tests as compared with the method of adding corpuscles and hemolysin separately.

Various methods have been proposed for the sensitization of corpuscles involving the amount of hemolysin used, the duration of sensitization and the temperature of exposure, all of which have some bearing upon the results of complement-fixation tests conducted with sensitized corpuscles.

In a preceding paper¹ we have shown that better results with complement-fixation tests are secured by titrating the complement and using the hemolysin and corpuscles as constants for adjustment of

*Investigation aided by funds accruing from the preparation of arsphenamine.

the hemolytic system, than by using the complement and corpuscles as constants and titrating the hemolysin. Comparatively little attention has been given, however, the subject of the technic for the titration of hemolysin, whereas several technical factors would appear of some importance in this connection.

PURPOSES OF INVESTIGATION

The purposes of this investigation were as follows:

1. A study of such technical factors concerned in the titration of hemolysin as (1) the influence of the amount of complement used; (2) the kind and duration of incubation and (3) the influence of the method of mixing the ingredients in conducting the titrations.

2. A study of methods for the sensitization of corpuscles.

3. A study of the influence exerted upon the results of syphilis complement-fixation tests by sensitized corpuscles as compared with tests conducted in the usual manner by adding corpuscles and hemolysin separately.

Part 1

TECHNICAL FACTORS CONCERNED IN THE TITRATION OF HEMOLYSIN

In the titration of hemolysin the results bear a direct and very important relation to the amount of complement used and the kind and duration of incubation; of these factors the first mentioned is of most importance.

Amount of Complement.—As is now well known, the use of a small amount of complement in the titration of hemolysin requires a large amount of hemolysin to produce complete hemolysis, whereas with a larger amount of complement the unit of hemolysin becomes progressively smaller. This is well shown in Table I in which an antsheep hemolysin was titrated with different amounts of complement and 0.2 c.c. of a 2.5 per cent suspension of sheep corpuscles; with 0.05 c.c. of 1:20 complement the unit of hemolysin was 0.1 c.c. of 1:2000 and with 0.5 c.c. complement the unit of hemolysin was but 0.1 c.c. of 1:60,000. *The point of practical importance is to use that amount of complement for the titration of hemolysin as will yield a unit of hemolysin which when employed for the routine and daily titration of complement will yield a unit of complement neither too large nor too small for the hemolytic system of the complement-fixation tests;* the importance of this was emphasized in the preceding

article¹ as having an important bearing upon the adjustment of the hemolytic system and the results of complement-fixation tests.

TABLE I
SHOWING THE RELATION OF THE AMOUNT OF COMPLEMENT TO THE
RESULTS OF HEMOLYSIN TITRATIONS

COMPLEMENT* 1:20 c.c.	UNIT OF HEMOLYSIN**
0.05	0.1 of 1:2000
0.1	0.1 of 1:9000
0.2	0.1 of 1:20000
0.3	0.1 of 1:30000
0.4	0.1 of 1:40000
0.5	0.1 of 1:60000

* Mixed sera of several guinea pigs.

** With 0.2 c.c. of 2.5 per cent suspension of sheep corpuscles and water-bath incubation of one hour.

It is well known that exact quantitative relations between hemolysin and complement do not exist and are not mathematically progressive; curiously if the unit of hemolysin is determined with a fixed amount of complement as for example, 1 c.c. of a 1:20 dilution, a back titration of the same complement with one unit of hemolysin will give a unit of complement smaller than the amount used for the titration of hemolysin, as for example, 0.8 c.c. and titration with two units of hemolysin reduces the unit of complement much more as for example, to 0.5 c.c. For the titration of hemolysin an arbitrary amount of complement must be used and the serum should be, of course, *a mixed serum from several guinea pigs* in order to average the hemolytic activity of different complement sera and the content of natural hemolysin; experience soon teaches what constitutes the average unit of complement best adapted for the complement-fixation technic being employed and this should be the fixed amount of complement employed for the titration of hemolysin in order to bring the units of complement sera on different days within the proper range. For example, if according to experience 0.1 to 0.3 c.c. of a dilution of complement represents the proper range within which the unit of complement should fall in order to secure best results, the hemolysin should be titrated with 0.2 c.c. of the same complement.

Occasionally guinea pig serum contains more than the average amount of natural antisheep hemolysin and when such serum is employed as complement the unit of hemolysin is reduced in amount accordingly; for example, the unit with hemolysin free complement has

been observed as 0.1 c.c. of 1:20,000 whereas with a complement containing natural hemolysin the unit of the same hemolysin was 0.1 c.c. of 1:50,000. In some laboratories and notably in those of the New York Board of Health, the serum of each guinea pig is tested for hemolysin and if present the serum is not used; we have found that this excludes a large percentage² unless traces are disregarded, and believe that the use of a mixture of sera removes the difficulty and especially if the hemolysin is titrated daily for the unit before titrating the complement.

THE KIND AND DURATION OF INCUBATION

In the titration of hemolysin the mixtures of hemolysin, complement and corpuscles are incubated either in a water-bath at 38° C. or in a thermostat at the same temperature; the time allowed for hemolysis varies with different workers from fifteen minutes to two hours. Wassermann advised the use of the thermostat for one hour, but several investigators have stated that this period is unnecessarily long, and especially if a water-bath is employed. It is commonly believed that one-half hour in a water-bath is equal to one hour in a thermostat (air incubation) and the former has become widely adopted.

The experiment shown in Table II is an example of the influence of time and kind of incubation upon the results of titration of anti-sheep hemolysin; water-bath incubation at 38° C. invariably gives more rapid hemolysis than thermostat incubation, one hour in the former being generally equal to one and a half hours in the latter.

While the unit of hemolysin is generally read at the end of one-half to one hour, hemolysis may not be completed in this time according to the technic employed; to reach the end point at least one-half hour in a water-bath and one hour in a thermostat were required for one method as shown in Table II and two and one-half and four hours, respectively, for a second method, both tests being conducted with the same complement serum and sheep corpuscles.

In Chart 1 are shown curves of hemolysis observed by titrating an antihuman hemolysin diluted 1:40 and an antisheep hemolysin 1:500 by water-bath and air incubation. The rate of hemolysis is greatly influenced by the amount of complement used, but in titrations which are strictly comparative, in order to elicit differences ascribable to the kind of incubation alone, the following have been observed: with

water-bath incubation hemolysis is from 50 to 75 per cent completed at the end of half an hour and generally completed or almost so at the end of one hour; with air incubation hemolysis is about 25 per cent complete at the end of half an hour and about 90 per cent completed at the end of one hour.

From the standpoint of economy in time the water-bath is to be preferred; for the same reason and more especially since hemolysis is practically over in the majority of titrations at the expiration of one hour, *an incubation of one hour in a water-bath at 38° C. appears quite satisfactory for the titration of hemolysin* inasmuch as the absolute end point in hemolysis is not necessary for a sufficiently close adjustment of the hemolytic system. As described in the preceding article¹ the question of time is of more importance in relation to the titration of complement and should not be unduly shortened at the expense of accuracy and delicacy in results.

Method of Mixing Ingredients in Hemolysin Titrations.—Very little or no difference in results of hemolysin titrations are found according to the manner of setting up hemolysin titrations provided two points are observed; namely, (1) to add complement to the mixtures of corpuscles and hemolysin at once and (2) to shake the mixtures well and at once to prevent irregular sensitization of the corpuscles. If the titration is set up by mixing the corpuscles and hemolysin followed by an interval of five minutes or more before the addition of complement, there is sufficient time for some sensitization of the cells which results in a smaller unit of hemolysin for complete hemolysis than observed when complement is added at once and before this preliminary sensitization occurs. If the corpuscles are added very slowly or if the mixtures of hemolysin, corpuscles and complement are not shaken, a portion of the corpuscles may absorb more than their share of hemolysin and yield an irregular and confusing result. Too great dilution with saline solution and the use of too narrow tubes giving a high column of fluid are to be avoided because they are likely to produce irregular results.

PRINCIPLES OF A STANDARDIZED METHOD FOR THE TITRATION OF HEMOLYSIN

1. Although it is the common practice to titrate the hemolysin only occasionally inasmuch as immune hemolysins are highly resistant antibodies and keep fairly well over long periods of time, we be-

TABLE II

THE INFLUENCE OF KIND AND TIME OF INCUBATION UPON THE
RESULTS OF HEMOLYSIN TITRATIONS

TIME	UNIT OF HEMOLYSIN*		UNIT OF HEMOLYSIN**	
	Water-bath	Thermostat	Water-bath	Thermostat
15 minutes	1:10,000	1:10,000	1:3,300	1:1,000
30 minutes	1:20,000	1:10,000	1:5,000	1:2,500
60 minutes	1:20,000	1:20,000	1:5,000	1:2,500
1½ hours	1:20,000	1:20,000	1:5,500	1:3,300
2 hours	1:20,000	1:20,000	1:5,500	1:3,300
2½ hours	1:20,000	1:20,000	1:10,000	1:3,300
3 hours	1:20,000	1:20,000	1:10,000	1:6,200
3½ hours	1:20,000	1:20,000	1:10,000	1:6,200
4 hours	1:20,000	1:20,000	1:10,000	1:10,000
4 hours plus refrigerator	1:20,000	1:20,000	1:10,000	1:10,000

* With 0.2 c.c. of 1:20 complement and 0.2 c.c. of 2.5% suspension of corpuscles.

** With 1.0 c.c. of 1:20 complement and 1.0 c.c. of 2.5% corpuscles.

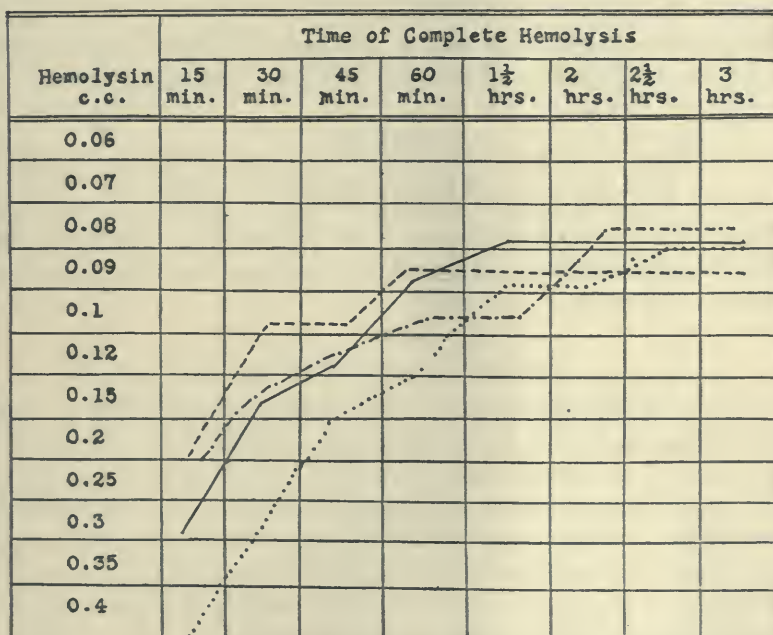


Chart 1. The rate of hemolysis in water-bath and air (thermostat) incubation.

— = antishoop with water-bath incubation.

..... = same antishoop with air incubation.

----- = antihuman hemolysin with water-bath incubation.

- . - . - = antihuman hemolysin with air incubation.

lieve that *better results are obtained by daily titrations in order to allow for the variable amounts of natural hemolysins in guinea pig sera, and especially if an antisheep hemolytic system is employed.*

2. Rabbit immune hemolytic sera are preserved with glycerine³ and progressive dilutions prepared with physiologic saline solution as 1:1000, 1:2000, 1:3000, 1:4000, etc. and used in constant amount of 0.1 or 1 c.c. with constant amounts of complement and corpuscle suspension; physiologic saline solution is added to bring the total volume to the same amount in each tube.

3. In setting up the titration, the complement is first placed in the tubes followed by the corpuscles and lastly by the graded amounts of hemolysin and sufficient saline solution; this order is followed in order to prevent the irregular sensitization of corpuscles described above.

4. Each tube is well shaken and the series placed in a water-bath at 38° C. for one hour; the smallest amount of hemolysin producing complete hemolysis is taken as the *unit*.

The details will be described in a succeeding paper setting forth the technic of the standardized method to be proposed.

Part 2

METHODS FOR THE SENSITIZATION OF CORPUSCLES

In this connection two factors are of importance; namely, the rapidity of sensitization at different temperatures, and the amount of hemolysin absorbed by corpuscles.

RAPIDITY OF SENSITIZATION

The general practice is to mix hemolysin and corpuscles at room temperature (about 20° C.) for one hour; Table III is an example of the results of numerous experiments with sheep corpuscles and anti-sheep hemolysin in which the rapidity and degree of sensitization were gauged and measured by the results of titrations with complement. In each experiment the same complement, corpuscles and hemolysin were employed and the unit of complement determined by titration in water-bath incubation for one hour.

As shown in Table III, sensitization is a very rapid process and particularly at ordinary room temperature (about 20° C.), being generally more rapid at this temperature than in a water-bath at

38° C. or in a refrigerator at 6 to 8° C. For the absorption of one unit of hemolysin, one-half hour at room temperature is generally sufficient; for the absorption of two to ten units at least forty-five minutes to one hour are required, as shown in Table IV.

TABLE III
THE INFLUENCE OF METHOD OF SENSITIZING SHEEP CORPUSCLES UPON
COMPLEMENT TITRATIONS

METHOD OF SENSITIZATION	UNIT OF COMPLEMENT*		UNIT OF COMPLEMENT**	
	Corpuscles sensitized with 1 unit of hemolysin	Corpuscles sensitized with 2 units of hemolysin	Corpuscles sensitized with 1 unit of hemolysin	Corpuscles sensitized with 2 units of hemolysin
15 min. in water-bath	0.22	0.12	0.3	0.2
30 min. in water-bath	0.22	0.08	0.24	0.16
1 hour in water-bath	0.2	0.08	0.22	0.16
15 min. at room temperature	0.22	0.1	0.2	0.2
30 min. at room temperature	0.12	0.06	0.18	0.1
1 hour at room temperature	0.12	0.06	0.16	0.1
4 hours at room temperature	0.12	0.06	0.16	0.1
1 hour in refrigerator	0.18	0.08	0.18	0.22
2 hours in refrigerator	0.18	0.08	0.16	0.18
4 hours in refrigerator	0.14	0.06	0.12	0.1

* First serum: Unit of complement titrated with plain corpuscles and 1 unit of hemolysin was 0.2 c.c. of 1:20 dilution; with 2 units of hemolysin, 0.1 c.c. of 1:20 dilution.

** Second serum: Unit of complement titrated with plain corpuscles and 1 unit of hemolysin was 0.24 c.c. of 1:20 dilution; with 2 units of hemolysin, 0.14 c.c. of 1:20 dilution.

TABLE IV
THE TIME REQUIRED FOR SENSITIZATION OF SHEEP CORPUSCLES AT
ROOM TEMPERATURE WITH VARYING AMOUNTS OF HEMOLYSIN

TIME OF SENSITIZATION	UNITS OF COMPLEMENT DILUTED 1:20 WITH CORPUSCLES SENSITIZED WITH			
	1 unit hemolysin	2 units hemolysin	4 units hemolysin	8 units hemolysin
5 minutes	0.2 c.c.	0.15 c.c.	0.12 c.c.	0.09 c.c.
15 minutes	0.15 c.c.	0.1 c.c.	0.1 c.c.	0.08 c.c.
30 minutes	0.15 c.c.	0.1 c.c.	0.1 c.c.	0.07 c.c.
45 minutes	0.15 c.c.	0.09 c.c.	0.09 c.c.	0.07 c.c.
60 minutes	0.15 c.c.	0.09 c.c.	0.09 c.c.	0.07 c.c.
1½ hours	0.15 c.c.	0.09 c.c.	0.09 c.c.	0.07 c.c.
2 hours	0.15 c.c.	0.09 c.c.	0.09 c.c.	0.07 c.c.

THE AMOUNT OF HEMOLYSIN ABSORBED BY SHEEP CORPUSCLES

For determining the amount of hemolysin absorbed by sheep corpuscles, washed cells were exposed to increasing amounts of hemolysin varying from one to a hundred units for one hour at 20° C; the corpuscles of each mixture were then secured by centrifuging, washed, re-suspended in saline solution and the degree of sensitization measured by complement titrations. The supernatant fluids secured by centrifuging the corpuscles from the hemolysin solutions were tested for unabsorbed hemolysin by adding sheep corpuscles and hemolysin-free complement.

The results of experiments similar to those given in Tables V and VI have shown that insofar as the results of complement titrations are concerned the maximum of sensitization is reached when sheep corpuscles are sensitized with four to six units of hemolysin, that is, corpuscles exposed to larger amounts of hemolysin do not become more sensitive to the hemolytic activity of complement. Morgenroth and Sachs⁴ have also found that sheep cells sensitized with at least five units of hemolysin represent the maximum degree of sensitization for guinea pig complement.

That sheep corpuscles, however, may absorb larger amounts of hemolysin and as much as twelve to twenty units at least, is indicated by the results of tests for unabsorbed hemolysin after the corpuscles have been removed by centrifuging (Tables V and VI); *the excess of hemolysin above four to six units, however, does not increase the susceptibility of sheep corpuscles to the hemolytic activity of guinea pig complement.*

Similar conditions appear to exist for ox cells, but experiments with human cells proved unsuccessful owing to the interference exerted by the hemagglutinins.

Part 3

THE INFLUENCE UPON THE RESULTS OF COMPLEMENT-FIXATION TESTS
CONDUCTED WITH PLAIN AND SENSITIZED CORPUSCLES

The Relative Susceptibility of Plain and Sensitized Corpuscles to Hemolysis.—It is well known that sensitized corpuscles are decidedly more susceptible to the hemolytic activity of complement than plain corpuscles exposed to the same amounts of hemolysin and complement; therefore the amount of complement required for the complete lysis of sensitized corpuscles is always less than required for an equal

TABLE V

THE AMOUNT OF HEMOLYSIN ABSORBED BY SHEEP CORPUSCLES AND
INFLUENCE UPON COMPLEMENT TITRATIONS

HEMOLYSIN USED FOR SENSITIZATION	COMPLEMENT TITRATIONS 1:10						HEMOLYSIN ABSORBED
	0.2	0.3	0.4	0.5	0.6	0.7	
1 unit*	S**	M	M	M	M	C	All
2 units	M	M	M	C	C	C	All
4 units	M	M	C	C	C	C	All
6 units	M	C	C	C	C	C	All
8 units	M	C	C	C	C	C	All
10 units	M	C	C	C	C	C	All
12 units	M	C	C	C	C	C	All
16 units	M	C	C	C	C	C	Partial

* Titrated with 1 c.c. of 1:10 complement and 1 c.c. of 5 per cent corpuscles; unit was 1 c.c. of 1:2000. Sensitization for one hour at 20° C.

** S = slight hemolysis; M = marked hemolysis; C = complete hemolysis.

TABLE VI

THE AMOUNT OF HEMOLYSIN ABSORBED BY SHEEP CORPUSCLES AND
INFLUENCE UPON COMPLEMENT TITRATIONS

AMOUNT OF HEMOLYSIN USED FOR SENSITIZATION	COMPLEMENT TITRATIONS 1:20					HEMOLYSIN ABSORBED
	0.08	0.09	0.1	0.12	0.15	
1 unit*	S	M	M	M	C	All
2 units	M	M	M	C	C	All
4 units	M	M	C	C	C	All
6 units	M	C	C	C	C	All
8 units	M	C	C	C	C	All
10 units	M	C	C	C	C	Partial
12 units	M	C	C	C	C	Partial

* Titrated with 0.2 c.c. of 1:20 complement and 0.2 c.c. of 2.5 per cent corpuscles; unit was 0.1 c.c. of 1:20,000. Sensitization for one hour at 20° C.

TABLE VII

THE HEMOLYTIC ACTIVITY OF COMPLEMENT FOR CORPUSCLES SENSITIZED WITH
ONE UNIT OF HEMOLYSIN FOR ONE HOUR AT 20° C.
AND FOR PLAIN CORPUSCLES

COMPLEMENT	UNIT OF COMPLEMENT*	
	With Plain Corpuscles	With Sensitized Corpuscles
Serum No. 1 diluted 1:20	0.2	0.12
Serum No. 2 diluted 1:20	0.5	0.4
Serum No. 3 diluted 1:20	0.24	0.16

* Corpuscles 0.2 c.c. of 2½ per cent suspension; 1 unit of hemolysin determined by titration with 0.2 c.c. of 1:20 complement.

amount of plain corpuscles in the presence of the same amount of hemolysin. Three examples from a series are shown in Table VII giving the smallest amounts of complement sera diluted 1:20, required for the complete lysis of 0.2 c.c. of 2.5 per cent suspensions of sheep corpuscles titrated in the presence of one unit of hemolysin and the amounts required for the same corpuscles after sensitization with the same hemolysin; in every instance the sensitized corpuscles required less complement for complete hemolysis. Similar results are shown in Tables III, IV, V, and VI. This fact is of fundamental importance in relation to the use of sensitized corpuscles for the conduct of complement-fixation tests when the complement is titrated with plain corpuscles and the tests conducted with sensitized corpuscles; under these conditions the hemolytic system may not be closely enough adjusted and tests conducted with corpuscles sensitized with one to six units of hemolysin are apt to be correspondingly less sensitive, because the amount of complement is excessive. For example, the unit of complement titrated with plain corpuscles and one unit of hemolysin may be 0.25 c.c., but only 0.2 c.c. when titrated with corpuscles previously sensitized with the same amount of hemolysin, 0.15 c.c. when the corpuscles are sensitized with two units of hemolysin and 0.09 c.c. with corpuscles sensitized with five units of hemolysin.

RESULTS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH PLAIN AND SENSITIZED CORPUSCLES AND A CONSTANT AMOUNT OF COMPLEMENT

In tests conducted according to the principles of Wassermann's technic, namely, with a constant amount of complement and two units of titrated hemolysin, the use of corpuscles previously sensitized with the hemolysin yields less sensitive reactions than tests in which the corpuscles and hemolysin are added separately. The reason is given above, namely, that sensitized corpuscles require less complement for complete lysis than the same amount of plain corpuscles in the presence of the same amount of hemolysin added separately.

These differences are most apparent in comparative tests employing graded amounts of each serum as shown in Table VIII; when large single doses of serum are employed the differences in degree of sensitiveness may not be apparent with strongly positive sera, but are strikingly so with weakly positive sera, as shown in Table IX. Furthermore, the differences are more apparent with plain than with cholesterolized antigens, because the latter absorb more complement and yield stronger complement-fixation reactions (Table IX).

TABLE VIII
COMPARATIVE SENSITIVENESS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH PLAIN AND SENSITIZED CORPUSCLES*

SERA	PLAIN CORPUSCLES**				CORPUSCLES SENSITIZED WITH 2 UNITS†				CORPUSCLES SENSITIZED WITH 4 UNITS				CORPUSCLES SENSITIZED WITH 10 UNITS			
	0.1	0.01	0.001	0.0001	0.1	0.01	0.001	0.0001	0.1	0.01	0.001	0.0001	0.1	0.01	0.001	0.0001
	S. C.				S. C.				S. C.				S. C.			
1	1†	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	2	1	-	-	-	1	-	-	1	-	-	-	1	-	-	-
3	3	2	-	-	-	3	-	-	1	-	-	-	-	-	-	-
4	4	3	1	-	-	2	-	-	1	-	-	-	-	-	-	-
5	4	3	-	-	-	1	-	-	-	-	-	-	-	-	-	-
6	4	3	-	-	-	4	-	-	3	2	-	-	-	-	-	-
7	3	1	-	-	-	1	-	-	-	-	-	-	-	-	-	-
8	4	3	1	-	-	3	1	-	4	2	-	-	4	1	-	-
9	4	3	1	-	-	4	3	-	1	-	-	-	1	-	-	-
10	1	1	-	-	-	1	-	-	-	-	-	-	-	-	-	-
11	1	1	-	-	-	1	-	-	-	-	-	-	-	-	-	-
12	4	4	4	-	-	4	4	-	4	4	3	-	4	4	3	-

* Complement used in constant amount of 1 c.c. of 1:20 dilution in both series of tests; cholesterolized heart extract employed in all tests.

** Hemolysin titrated and used in two units.

† Corpuscles sensitized for one hour at 20°C.

‡ 4 = ++++ strongly positive; 3 = +++ moderately positive; 2 = ++ weakly positive; 1 = + very weakly positive; -- = negative.

TABLE IX
COMPARATIVE SENSITIVENESS OF COMPLEMENT-FIXATION TESTS CONDUCTED
WITH PLAIN AND SENSITIZED CORPUSCLES*

SERA	PLAIN CORPUSCLES**				SENSITIZED CORPUSCLES†			
	Antigen 1	Antigen 2	Antigen 3	Control	Antigen 1	Antigen 2	Antigen 3	Control
1	4††	4	4	—	4	4	4	—
2	3	1	1	—	3	—	—	—
3	2	1	1	—	1	—	—	—
4	4	3	1	—	3	1	—	—
5	4	4	4	—	4	4	4	—
6	4	4	4	—	4	4	4	—
7	4	3	—	—	3	1	—	—
8	1	—	—	—	—	—	—	—
9	2	1	1	—	1	—	—	—
10	4	3	3	—	4	2	1	—
11	3	2	1	—	2	1	—	—
12	4	3	2	—	4	1	—	—
13	4	2	2	—	4	1	1	—
14	4	3	3	—	4	2	2	—
15	4	4	4	—	4	4	4	—
16	4	3	2	—	4	1	—	—
17	3	2	1	—	2	1	—	—
18	3	2	2	—	3	—	—	—
19	4	1	1	—	2	—	—	—
20	4	3	3	—	4	1	1	—

* Complement used in constant amount of 1 c.c. of 1:20 dilution in both series of tests.

** Hemolysin titrated and used in two units.

† Corpuscles sensitized with 2 units of hemolysin for 1 hour at 20° C.

‡ Antigen 1 = cholesterolized heart extract; antigen 2 = alcoholic extract syphilitic liver; antigen 3 = acetone insoluble lipoids.

†† 4 = ++++ strongly positive; 3 = +++ moderately positive; 2 = ++ weakly positive; 1 = + very weakly positive; — = negative.

A summary of the results of comparative tests conducted with fixed amounts of complement and plain and sensitized corpuscles is given in Table X; *practically in every instance the tests conducted with sensitized corpuscles yielded weaker reactions than duplicate tests with the same amounts of corpuscles and hemolysin added separately*; tests conducted with sensitized corpuscles also yielded a higher percentage of falsely negative reactions with syphilitic sera.

RESULTS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH PLAIN AND
SENSITIZED CORPUSCLES AND TWO UNITS OF COMPLEMENT
TITRATED WITH PLAIN CORPUSCLES

As previously reported¹ tests conducted with two units of titrated complement are more sensitive than tests conducted with a fixed amount of complement and two units of titrated hemolysin; comparative tests conducted with plain and sensitized corpuscles, graded amounts of serum, two units of complement determined by titration

TABLE X
A SUMMARY OF RESULTS OF COMPARATIVE COMPLEMENT-FIXATION TESTS CONDUCTED WITH PLAIN AND SENSITIZED CORPUSCLES
IN WHICH THE HEMOLYSIN WAS TITRATED AND THE COMPLEMENT USED IN A CONSTANT AMOUNT

METHOD OF SENSITIZING CORPUSCLES	SYPHILITIC SERA TESTED	RESULTS COMPARED WITH REACTIONS CONDUCTED WITH PLAIN CORPUSCLES			NEGATIVE REACTIONS WITH SENSITIZED CELLS; POSITIVE WITH PLAIN CELLS
		Reactions of Equal Degree	Stronger Reac- tions with Plain Corpuscles	Stronger Reac- tions with Sen- sitized Corpuscles	
1 unit hemolysin; 5 hours in refrigerator	9	1	8	none	none
1 unit hemolysin; 1 hour in water-bath	52	25	25	none	2
2 units hemolysin; 1 hour in room	12	5	6	none	1
4 units hemolysin; 1 hour in room	12	none	8	none	4
10 units hemolysin; 1 hour in room	12	none	4	none	8
2 units hemolysin; 1 hour in room	85	58	23	none	4
1 unit hemolysin; 8 hours in refrigerator	18	11	7	none	none

with plain corpuscles and one unit of hemolysin are shown in Tables XI and XII. In the results given in Table XI the tests were conducted with a primary incubation of one hour in a water-bath and those given in Table XII were observed with four hours in a refrigerator at 6° C. and one hour in a water-bath.

TABLE XI
COMPARATIVE SENSITIVENESS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH
PLAIN AND SENSITIZED CORPUSCLES; PRIMARY INCUBATION
1 HOUR AT 38° C. (WATER-BATH)*

SERA	TESTS CONDUCTED WITH PLAIN CORPUSCLES						TESTS CONDUCTED WITH SENSITIZED CORPUSCLES**					
	0.1	0.025	0.006	0.0015	0.0004	Control	0.1	0.025	0.006	0.0015	0.0004	Control
1	4	4	4	3	-	-	4	4	4	1	-	-
2	4	4	3	1	-	-	4	4	3	1	-	-
3	3	3	-	-	-	-	3	3	-	-	-	-
4	4	4	1	-	-	-	3	3	1	-	-	-
5	3	3	1	-	-	-	3	-	-	-	-	-
6	4	4	-	-	-	-	4	4	-	-	-	-
7	4	4	1	-	-	-	3	3	-	-	-	-
8	1	1	-	-	-	-	1	1	-	-	-	-
9	2	1	-	-	-	-	1	-	-	-	-	-
10	4	4	1	-	-	-	3	2	-	-	-	-
11	3	3	-	-	-	-	3	3	-	-	-	-
12	4	4	1	-	-	-	4	3	-	-	-	-
13	4	4	3	1	-	-	4	4	1	-	-	-
14	4	4	4	4	1	-	4	4	4	3	1	-
15	4	4	1	-	-	-	4	3	-	-	-	-
16	1	-	-	-	-	-	-	-	-	-	-	-
17	4	4	4	1	-	-	4	4	4	1	-	-
18	4	4	4	2	-	-	4	4	4	1	-	-
19	4	4	4	3	1	-	4	4	4	2	-	-
20	4	4	4	3	2	-	4	4	4	-	-	-

* Complement titrated with 1 unit of hemolysin and 0.2 c.c. of 2.5 per cent suspension of plain corpuscles and 2 units used in both series of tests.

** Corpuscles sensitized with 1 unit of hemolysin for 1 hour at 20° C.

TABLE XII
COMPARATIVE SENSITIVENESS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH
PLAIN AND SENSITIZED CORPUSCLES; PRIMARY INCUBATION
4 HOURS AT 6° C. AND 1 HOUR AT 38° C. (WATER-BATH)*

SERA	TESTS CONDUCTED WITH PLAIN CORPUSCLES						TESTS CONDUCTED WITH SENSITIZED CORPUSCLES**					
	0.1	0.025	0.006	0.0015	0.0004	Control	0.1	0.025	0.006	0.0015	0.0004	Control
1	3	3	1	-	-	-	3	2	-	-	-	-
2	4	4	4	3	-	-	4	4	4	1	-	-
3	4	4	4	3	1	1	4	4	4	1	-	-
4	4	4	4	2	1	-	4	4	4	1	-	-
5	4	4	4	2	1	-	4	4	3	-	-	-
6	4	4	3	-	-	-	4	4	1	-	-	-

* Complement titrated with plain corpuscles and used in both series of tests in two units.

** Corpuscles sensitized with 1 unit of hemolysin for 5 hours at 6° C.

As shown in the tables the differences in results of these tests conducted with plain and sensitized corpuscles are much less marked than described above with tests in which the complement was not titrated but used in one constant amount; with the larger amounts of patients' serum the results were closely similar but differences were usually apparent with the smaller amounts, *the tests with corpuscles sensitized with one unit of hemolysin being less sensitive than similar tests in which the corpuscles and one unit of hemolysin were added separately.*

RESULTS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH TWO UNITS OF COMPLEMENT TITRATED WITH PLAIN CORPUSCLES AND WITH TWO UNITS OF COMPLEMENT TITRATED WITH SENSITIZED CORPUSCLES

Under these conditions tests conducted with sensitized corpuscles may yield reactions more nearly equal in sensitiveness to those conducted with plain corpuscles. The reason is apparent; the unit of complement being adjusted to the sensitized corpuscles is smaller than the unit obtained with plain corpuscles and an excess of complement is thereby avoided in conducting the complement-fixation tests.

Table XIII gives the results of comparative tests with ten syphilitic sera in graded amounts; the complement was titrated with plain sheep corpuscles and used in two units (0.5 c.c. of 1:20) with

TABLE XIII
COMPARATIVE SENSITIVENESS OF COMPLEMENT-FIXATION TESTS WITH TEN SYPHILITIC SERA CONDUCTED WITH PLAIN AND SENSITIZED CORPUSCLES AND TITRATED COMPLEMENT

SERA	WITH PLAIN CORPUSCLES*						WITH SENSITIZED CORPUSCLES**					
	0.1	0.02	0.006	0.001	0.0004	Control	0.1	0.02	0.006	0.001	0.0004	Control
1	4†	4	—	—	—	—	4	4	1	—	—	—
2	4	4	2	—	—	—	4	4	2	1	—	—
3	4	4	1	—	—	—	4	4	2	1	—	—
4	4	4	4	3	—	—	4	4	4	3	1	—
5	4	4	4	3	1	—	4	4	4	3	1	—
6	4	4	4	1	—	—	4	4	4	3	—	—
7	4	2	—	—	—	—	4	4	1	1	—	—
8	4	3	—	—	—	—	4	4	2	1	—	—
9	4	4	3	—	—	—	4	4	3	—	—	—
10	4	4	4	—	—	—	4	4	4	3	—	—

* Unit of complement was 0.25 of 1:20 dilution; two units employed with one unit of hemolysin.

** Corpuscles sensitized with 4 units of hemolysin for 1 hour at 20° C; unit of complement was 0.15 of 1:20 dilution; 2 units employed.

† 4 = ++++ strongly positive; 3 = +++ moderately positive; 2 = ++ weakly positive; 1 = + very weakly positive; — = negative.

TABLE XIV
COMPARATIVE SENSITIVENESS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH PLAIN AND
SENSITIZED CORPUSCLES AND TITRATED COMPLEMENT

SERA	PLAIN CORPUSCLES*				CORPUSCLES SENSITIZED WITH 1 UNIT**				CORPUSCLES SENSITIZED WITH 2 UNITS†			
	0.1	0.02	0.06	0.001	0.0004	Control	0.1	0.02	0.06	0.001	0.0004	Control
1	4	4	4	-	-	-	4	4	4	-	-	-
2	4	4	2	1	1	1	4	4	4	-	-	-
3	4	4	1	1	1	-	4	4	4	1	-	-
4	4	4	2	1	1	-	4	4	3	1	-	-
5	4	4	3	1	1	-	4	4	4	3	-	-
6	2	1	-	-	-	-	1	1	1	-	-	-
7	4	4	4	3	1	-	4	4	4	-	-	-
8	4	3	1	-	-	-	4	4	2	4	-	-
9	4	4	1	-	-	1	3	3	3	-	-	-
10	3	2	1	-	-	-	3	3	3	-	-	-
11	3	3	-	-	-	-	3	1	1	-	-	-
12	4	4	2	1	-	-	2	3	2	1	-	-
13	4	4	1	-	-	-	4	4	4	-	-	-
14	4	4	3	-	-	-	4	4	4	-	-	-
15	4	4	-	-	-	-	4	4	4	-	-	-

*Unit of complement 0.25 c.c. of 1:20.

**Unit of complement 0.2 c.c. of 1:20.

†Unit of complement 0.2 c.c. of 1:20.

4 = ++++ strongly positive; 3 = +++ moderately positive; 2 = ++ weakly positive; 1 = + very weakly positive; - = negative.

TABLE XIV—Continued

SERA	CORPUSCLES SENSITIZED WITH 4 UNITS*						CORPUSCLES SENSITIZED WITH 6 UNITS**						CORPUSCLES SENSITIZED WITH 10 UNITS†											
	0.1		0.02		0.006		0.001		0.0004		Control		0.1		0.02		0.006		0.001		0.0004		Control	
	4	3	4	4	4	4	-	-	-	-	-	-	4	4	4	4	4	4	4	4	4	4	4	4
1	4	3	4	4	4	4	-	-	-	-	-	-	4	4	3	4	4	4	4	4	4	4	4	-
2	3	4	4	4	4	4	-	-	-	-	-	-	3	4	4	4	4	4	4	4	4	4	4	-
3	4	4	4	4	4	4	-	-	-	-	-	-	4	4	4	4	4	4	4	4	4	4	4	-
4	4	4	4	4	4	4	-	-	-	-	-	-	4	4	4	4	4	4	4	4	4	4	4	-
5	4	4	4	4	4	4	-	-	-	-	-	-	4	4	4	4	4	4	4	4	4	4	4	-
6	1	1	4	4	4	4	-	-	-	-	-	-	1	1	4	4	4	4	4	4	4	4	4	-
7	4	3	4	4	4	4	-	-	-	-	-	-	4	4	4	4	4	4	4	4	4	4	4	-
8	3	4	4	4	4	4	-	-	-	-	-	-	3	3	4	4	4	4	4	4	4	4	4	-
9	4	3	4	4	4	4	-	-	-	-	-	-	3	3	3	3	3	3	3	3	3	3	3	-
10	3	4	4	4	4	4	-	-	-	-	-	-	3	3	3	3	3	3	3	3	3	3	3	-
11	2	2	4	4	4	4	-	-	-	-	-	-	2	2	3	3	3	3	3	3	3	3	3	-
12	2	1	4	4	4	4	-	-	-	-	-	-	2	1	1	1	1	1	1	1	1	1	1	-
13	2	2	4	4	4	4	-	-	-	-	-	-	2	2	2	2	2	2	2	2	2	2	2	-
14	4	3	4	4	4	4	-	-	-	-	-	-	4	4	3	4	4	4	4	4	4	4	4	-
15	4	4	4	4	4	4	-	-	-	-	-	-	4	4	4	4	4	4	4	4	4	4	4	-

* Unit of complement 0.15 c.c. of 1:20; ** Unit of complement 0.15 c.c. of 1:20; † Unit of complement 0.15 c.c. of 1:20.

one unit of hemolysin and duplicate tests were conducted with two units of complement (0.3 c.c. of 1:20) titrated with the corpuscles after sensitization with four units of hemolysin. The latter tests were even more sensitive than those conducted with plain corpuscles and probably because of the smaller amount of complement employed.

In Table XIV are shown the results of comparative tests with 15 syphilitic sera tested in graded amounts with plain and sensitized sheep corpuscles, the complement being titrated with the plain and each lot of sensitized corpuscles and two units employed in the main tests. As shown in the table the unit of complement with plain cells and one unit of hemolysin was 0.25 c.c. of 1:20 dilution; with corpuscles sensitized with one unit of hemolysin the unit was 0.2 c.c.; with corpuscles sensitized with two units, 0.2 c.c. and with four, six and ten units 0.15 c.c.

These results are examples of similar tests with a large number of syphilitic sera; while tests conducted with sensitized corpuscles may be of equal or even greater delicacy than duplicate tests conducted with plain corpuscles as shown in Table XIII, generally the tests conducted with sensitized corpuscles are somewhat less sensitive, as shown in Table XIV. A great deal depends upon the size of the unit of complement, but when two units are employed in complement-fixation tests sensitized corpuscles are more susceptible to the hemolytic activity of any free or unfixed complement than plain corpuscles, and consequently show a somewhat greater degree of hemolysis.

These differences in sensitiveness of reactions are best demonstrated in tests employing graded amounts of serum; when but one dose of serum is employed the results may be strikingly similar.

If complement-fixation tests are conducted with sensitized corpuscles for the sake of convenience, it is imperative to titrate the complement rather than to use a constant or fixed dose, and furthermore, *the complement should be titrated with the sensitized rather than with plain corpuscles.*

THE SUSCEPTIBILITY OF SENSITIZED CORPUSCLES TO THE INFLUENCE OF FREE HEMOLYSIN

Of additional importance in relation to a decision upon the use of plain or sensitized corpuscles for complement-fixation tests, is the probable influence of natural hemolysins in the sera being tested

upon the occurrence and degree of hemolysis. In other words, are tests conducted with sensitized sheep corpuscles subject to the influence of natural antishcep hemolysin to the same degree as tests conducted with plain corpuscles?

As stated above when sheep corpuscles are sensitized with four to six units of hemolysin, the maximum degree of susceptibility to the hemolytic activity of complement is reached; accordingly it would appear that in tests conducted with corpuscles sensitized with four to six units of hemolysin, an excess of free hemolysin in the patient's serum would not enhance the degree of hemolysis. Actual experiments have shown that this is true; in Tables XV and XVI are given the results of titrations of complement with plain sheep corpuscles and corpuscles sensitized with one to ten units of hemolysin; these titrations were conducted in the presence of one to six units of free hemolysin placed in the tubes of each series. As shown in these tables the degree of hemolysis with corpuscles sensitized with one, two and three units of hemolysin is increased in the presence of free or additional hemolysin, whereas with corpuscles sensitized with more than four units of hemolysin the degree of hemolysis is not influenced by the presence of as much additional hemolysin as six units, which is much greater than the amount encountered in the form of natural antishcep hemolysin in a person's serum.

To determine this more definitely several syphilitic sera were tested in graded amounts by using each serum hemolysin free and repeating by adding immune hemolysin to each tube in amounts varying from one to ten units to represent natural hemolysin; the results observed with one serum are given in Table XVII. As will be seen by examination of this table, the addition of free hemolysin greatly

TABLE XV
THE SUSCEPTIBILITY OF SENSITIZED CORPUSCLES TO HEMOLYSIN

CORPUSCLES	UNITS OF COMPLEMENT WHEN TITRATED IN THE PRESENCE OF:			
	1 unit hemolysin	2 units hemolysin	4 units hemolysin	6 units hemolysin
Sensitized with 1 unit*	0.09	0.09	0.07	0.07
Sensitized with 2 units	0.09	0.08	0.07	0.06
Sensitized with 3 units	0.08	0.07	0.07	0.07
Sensitized with 4 units	0.07	0.07	0.07	0.07
Sensitized with 6 units	0.07	0.07	0.07	0.07
Sensitized with 8 units	0.07	0.07	0.07	0.07

* Unit of hemolysin 0.1 c.c. of 1:30,000 dilution; sensitization at 20° C. for one hour.

TABLE XVI
THE SUSCEPTIBILITY OF SENSITIZED CORPUSCLES TO HEMOLYSIS

CORPUSCLES	UNITS OF COMPLEMENT WHEN TITRATED IN THE PRESENCE OF:					
	No hemolysin	1 unit* hemolysin	2 units hemolysin	4 units hemolysin	6 units hemolysin	10 units hemolysin
Plain	0	0.4	0.3	0.2	0.15	0.15
Sensitized with 1 unit*	0.15	0.07	0.07	0.06	0.06	0.06
Sensitized with 2 units	0.07	0.06	0.06	0.04	0.04	0.04
Sensitized with 4 units	0.05	0.05	0.05	0.05	0.05	0.05
Sensitized with 6 units	0.05	0.05	0.05	0.05	0.06	0.06
Sensitized with 8 units	0.05	0.05	0.05	0.05	0.06	0.06
Sensitized with 10 units	0.05	0.05	0.05	0.05	0.06	0.06

* Unit of hemolysin 0.1 c.c. of 1:20,000 dilution; sensitization at 20° C. for one hour.

influenced the tests with plain corpuscles and corpuscles sensitized with one unit of hemolysin, but exerted much less influence upon tests with corpuscles sensitized with two units of hemolysin, still less with corpuscles sensitized with four units and not at all with corpuscles sensitized with six and ten units.

These results indicate, therefore, the advisability of sensitizing corpuscles with four to six units of hemolysin instead of one or two if sensitized corpuscles are employed in complement-fixation tests, in order to reduce the influence upon hemolysis of free or natural hemolysin in human sera.

THE DISSOCIATION OF HEMOLYSIN

As Muir has shown, hemolysin absorbed by corpuscles may become dissociated or free, and this may have some bearing upon the use of corpuscles sensitized with less than four units of hemolysin, if the dissociated hemolysin is active and capable of representing an excess and thereby enhancing hemolysis. In our experiments we found that dissociation of hemolysin occurred with corpuscles sensitized with six or more units of hemolysin when the washed cells were suspended in saline solution and incubated in a water-bath at 38° C. for one-half to four hours.

The experiment shown in Table XVIII was conducted by sensitizing sheep corpuscles with one, two, four, six and ten units of hemol-

TABLE XVII
THE INFLUENCE OF AN EXCESS OF HEMOLYSIN UPON COMPLEMENT-FIXATION TESTS CONDUCTED WITH PLAIN AND SENSITIZED CORPUSCLES AND TITRATED COMPLEMENT

SYPHILITIC SERUM	PLAIN CORPUSCLES**			CORPUSCLES SENSITIZED WITH 1 UNIT†			CORPUSCLES SENSITIZED WITH 2 UNITS‡		
	0.1	0.02	0.006	0.001	0.0004	0.1	0.02	0.006	0.001
No hemolysin	4	2	-	-	-	4	2	-	-
1 unit hemolysin*	4	2	-	-	-	3	1	-	-
2 units hemolysin*	4	4	-	-	-	3	3	-	-
4 units hemolysin*	3	1	-	-	-	3	-	-	-
6 units hemolysin*	3	-	-	-	-	2	2	-	-
10 units hemolysin*	2	-	-	-	-	2	-	-	-

* Added to each of the five tubes of the complement-fixation test carrying 0.1, 0.02, 0.006, 0.001 and 0.0004 c.c. serum.

** Unit of complement 0.4 c.c. 1:20; † 0.3 c.c. 1:20; ‡ 0.15 c.c. 1:20.

TABLE XVII—Continued

SYPHILITIC SERUM	CORPUSCLES SENSITIZED WITH 4 UNITS††			CORPUSCLES SENSITIZED WITH 6 UNITS‡‡			CORPUSCLES SENSITIZED WITH 10 UNITS=		
	0.1	0.02	0.006	0.001	0.0004	0.1	0.02	0.006	0.001
No hemolysin	4	4	-	-	-	4	4	-	-
1 unit hemolysin*	4	3	-	-	-	4	4	-	-
2 units hemolysin*	4	3	-	-	-	4	4	-	-
4 units hemolysin*	4	3	-	-	-	4	4	-	-
6 units hemolysin*	4	3	-	-	-	4	4	-	-
10 units hemolysin*	4	3	-	-	-	4	3	-	-

* Added to each of the five tubes of the complement-fixation test carrying 0.1, 0.02, 0.006, 0.001 and 0.0004 c.c. serum.

†† 0.15 c.c. 1:20; ‡‡ 0.1 c.c. 1:20; = 0.1 c.c. 1:20.

ysin for one hour at room temperature followed by six washings with saline to remove all traces of unbound hemolysin. These sensitized cells were then resuspended in saline and placed in a water-bath; at varying intervals portions were centrifuged and the supernatant fluids tested for hemolysin by adding plain sheep corpuscles and an excess of hemolysin-free guinea pig complement.

TABLE XVIII
THE DISSOCIATION OF HEMOLYSIN FROM SHEEP CORPUSCLES SENSITIZED
WITH ONE TO TWENTY UNITS OF HEMOLYSIN

SENSITIZATION	DISSOCIATION OF HEMOLYSIN*			
	½ hour	1 hour	2 hours	4 hours
With one unit	None	None	None	None
With two units	None	None	None	None
With four units	None	None	None	None
With six units	None	None	Slight	Slight
With twenty units	Marked	Marked	Slight	None

* Washed sensitized corpuscles suspended in saline and kept in a water-bath at 38° C.

The results are given in Table XVIII; curiously dissociation occurred rather rapidly and corpuscles suspended in saline for two to four hours yielded less dissociated hemolysin than corpuscles suspended for one-half to two hours; these results may be ascribed to the destruction of the released hemolysin by heat during the longer periods of exposure of the sensitized cells or to a reunion of the dissociated hemolysin with the corpuscles.

SUMMARY AND CONCLUSIONS

1. In the titration of hemolysin the unit or measure of activity varies greatly according to the amount of complement used, the amount of natural hemolysin in the complement, the kind and duration of incubation and to some extent according to the manner of mixing hemolysin, cells and complement.

2. The proper amount of complement to employ for the titration of hemolysin is the average amount found best by experience as the unit for conducting the complement-fixation test.

3. The use of a mixture of guinea pig sera for complement is generally a satisfactory adjustment for the natural hemolysins present and especially if the hemolysin is titrated daily before the titration of complement.

4. An incubation of one hour in a water-bath at 38° C. is generally satisfactory for determining the unit of hemolysin; one-half hour is too brief and over one hour unnecessarily long, as the absolute end point of hemolysis is not required.

5. In setting up the hemolysin titration the cells and hemolysin should not be left in contact before the addition of complement, because irregular sensitization of the cells may occur; in practice it appears best to pipette the complement followed by the corpuscles and lastly by the hemolysin and saline solution.

6. Sensitization of corpuscles was best accomplished by mixing corpuscles and hemolysin at ordinary room temperature for one hour.

7. While sheep corpuscles may absorb twelve or more units of hemolysin, the absorption of more than four to six units does not increase their susceptibility to the hemolytic activity of complement.

8. Sensitized corpuscles are more susceptible to the hemolytic activity of complement than plain corpuscles in the presence of the same amount of hemolysin; therefore in complement-fixation tests if any complement remains unfixed by syphilis antibody and the extract, the degree of hemolysis will be greater when sensitized corpuscles are added and the reactions consequently less sensitive than when plain corpuscles and hemolysin are added separately. This explains the following:

(a) In complement-fixation tests conducted with an arbitrary and fixed amount of complement as in Wassermann's method, the use of corpuscles sensitized with two units of hemolysin yielded less sensitive reactions than tests in which the plain corpuscles and hemolysin were added separately.

(b) When complement was titrated with plain corpuscles and two units used in comparative complement-fixation tests with plain and sensitized corpuscles, the tests with sensitized corpuscles generally yielded less sensitive reactions.

(c) When comparative complement-fixation tests were conducted with two units of complement titrated with plain corpuscles and two units titrated with the sensitized corpuscles, the reactions were more nearly equal in sensitiveness, although the tests with plain corpuscles were generally more sensitive. Under these conditions the unit of complement with sensitized corpuscles was less than with plain corpuscles and consequently the reactions with sensitized corpuscles were rendered more delicate than those in which sensitized corpuscles

were used with a constant arbitrary amount of complement as in "a," or with complement titrated with plain corpuscles as in "b."

9. Corpuscles sensitized with four to six units of hemolysin are not susceptible to the influence of natural hemolysins in complement and patients' sera and if sensitized corpuscles are employed in the conduct of complement-fixation tests it would appear advisable to sensitize with five units of hemolysin rather than with two units as is the usual custom.

10. Sensitized human corpuscles could not be used because of the occurrence of agglutination with the majority of rabbit antihuman hemolytic sera.

11. Demonstrable dissociation of hemolysin from corpuscles was not found unless the cells were sensitized with six or more units of hemolysin; under these conditions dissociation was evident within half an hour. Accordingly dissociation of hemolysin does not constitute a contraindication to the use of sensitized corpuscles.

12. The principles of a standardized technic for the titration of hemolysin are given; the details of the titration and the amount of hemolysin recommended for the conduct of a standardized complement-fixation technic will be published later.

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STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. XIII*

THE INFLUENCE OF HEATING SERUM UPON COMPLEMENT FIXATION IN SYPHILIS

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WHILE in the original Wassermann test each serum is "inactivated" by heating at 56° C. for thirty minutes, numerous modifications have been described in which unheated serum is used for the purpose of securing more sensitive reactions or for economy and greater simplicity in technic. Originally Wassermann and his associates advised the heating of sera for the main purpose of destroying the native complements and hence the phrase "inactivation of serum" has come into general use, but at the present time it is known that sera are heated for additional and probably more important reasons.

The subject is one of primary importance in relation to complement-fixation tests by reason of having a direct bearing upon the sensitiveness and specificity of the reactions; questions of economy of materials and time and of simplicity in technic are certainly of lesser importance.

CLASSIFICATION OF TESTS EMPLOYING UNHEATED OR RAW SERUM

These may be divided into three main classes as follows:

1. Tests of the nature of those of the original Noguchi test employing unheated serum, ignoring the presence of native complement and using guinea-pig complement.
2. Tests as those of Tschernogubow, Emery, Thompson, Ronchese, Noguchi homohemolytic, Bronfenbrenner and Schlesinger and Stern in which the native complements in the unheated serum of each patient are utilized.

*This investigation was aided by funds accruing from the preparation of arsphenamine.

3. Tests as those of Tschernogubow, Foix, Hecht, Flemming, Gradwohl, Bruce, Seelman, Bartlett and O'Shansky in which the native complements and certain natural hemolysins (anti-guinea pig and anti-sheep) in the unheated serum of each patient are utilized.

ADVANTAGES AND DISADVANTAGES OF TESTS EMPLOYING UNHEATED OR RAW SERUM

These have been discussed in a former paper of this series¹ bearing upon comparative studies of human and guinea pig complements for the conduct of a standardized complement-fixation test, and for the purposes of the present study only the important ones require repeating:

1. The *main advantage* is greater sensitiveness due to the fact that none of the antibody concerned in complement-fixation is lost or destroyed; furthermore in those tests employing the native complement of each serum the reactions may be stronger because human complement is somewhat more fixable than guinea pig complement and at the same time more susceptible to the anticomplementary influences of serum and antigen alone, which tends to increase the degree of complement absorption or fixation.

2. The *main disadvantage* is the fact attested to by Seligman and Pinkus², Noguchi³, Browning and McKenzie⁴ and numerous other investigators, that unheated or raw serum may yield falsely positive or nonspecific reactions; there appears to be conclusive evidence that tests conducted with the raw sera of healthy individuals or of persons suffering with diseases other than syphilis, yaws and leprosy are open to this serious objection. Noguchi has designated these reactions as "proteotropic" on the basis of his belief that they are due to the absorption or fixation of complement by something in unheated nonsyphilitic serum and a lipo-protein substance in the extract used as antigen; for this reason he advises the use of protein-free antigens, as his extracts of acetone insoluble lipoids. Whether or not this is the true explanation it would appear as conclusively proved that unheated serum may yield these nonspecific reactions, whereas heated sera do not.

Other advantages of using raw serum in some tests are economy, inasmuch as guinea pig complement is unnecessary and the tests usually simpler and less time-consuming; other disadvantages are the variation in fixability of human complement, the necessity for

using fresh sera, the 2 to 10 per cent of human sera deficient in complement, natural hemolysins or both¹, and the impossibility of testing cerebrospinal fluids. The disadvantages therefore, outweigh and outnumber the advantages and for this reason the conclusion has been reached that human complement cannot be utilized in a standardized Wassermann test.

PURPOSES OF INVESTIGATION

On the other hand, as previously stated, a standardized test must aspire to the sensitiveness of methods employing unheated sera insofar as specific reactions are concerned; it would appear advisable therefore, to study the influence of heating sera for the purpose of determining the *minimum amount of heat* required for the purpose of removing the native complements, anticomplementary substances and the substance responsible for the proteotropic reaction with the least destruction of syphilis antibody; accordingly the purposes of this study were as follows:

1. To determine how much heating is required to inactivate the native complements of human sera.
2. To determine how much heating is required to remove the anticomplementary substances of human sera.
3. To determine how much heating is required to remove the property of sera giving nonspecific or proteotropic reactions.
4. To study the influences of heating syphilitic serum upon the antibody concerned in the Wassermann reaction.

Part 1

THE INFLUENCE OF HEAT UPON HEMOLYTIC COMPLEMENT

The hemolytic complements of human and guinea pig sera are very susceptible to heat and readily inactivated; most interest centers in the complements of human sera in relation to the amount of heat required for inactivation in preparation for complement fixation tests.

When fresh human sera are heated in a water bath at 56° C. the complement activity is reduced almost eight times in five minutes (Tables I and II); inactivation begins even at 40° C. and becomes progressively greater as the temperature approaches 55° C. (Table III) but most destruction occurs with temperatures of over 50° C. As shown in Table I, the hemolytic activity of human complement may be reduced only one half after heating at 50° C. for thirty minutes, whereas 55° C. activity is reduced eight times in five minutes.

TABLE I
THE INFLUENCE OF HEAT UPON HUMAN COMPLEMENT

SERA	HEAT	UNITS OF COMPLEMENT* WITH SERA UNHEATED AND HEATED FOR:						
		UN-HEATED	1 MIN.	3 MIN.	5 MIN.	10 MIN.	15 MIN.	30 MIN.
1	55 C.	0.04	0.05	0.06	more than 0.3	more than 0.3	more than 0.3	more than 0.3
1	50 C.	0.04	0.04	0.04	0.04	0.04	0.06	0.08
2	55 C.	0.04	0.06	0.09	more than 0.3	more than 0.3	more than 0.3	more than 0.3
2	50 C.	0.04	0.04	0.04	0.04	0.06	0.08	0.1

*Smallest amounts of serum producing complete hemolysis of 0.1 c.c. of a 5 per cent suspension of human corpuscles with 0.5 c.c. of 1:40 antihuman hemolysin.

TABLE II
THE INFLUENCE OF HEATING HUMAN COMPLEMENT AT 56°C. IN A WATER-BATH

SERA	UNITS OF COMPLEMENT*		
	BEFORE	1 MINUTE	5 MINUTES
1	0.03	0.04	more than 0.05
2	0.03	0.03	more than 0.05
3	0.02	0.03	more than 0.05
4	0.03	0.05	more than 0.05
5	0.03	0.05	more than 0.05
6	0.02	0.03	more than 0.05
7	0.03	0.04	more than 0.05
8	0.02	0.03	more than 0.05
9	0.03	0.05	more than 0.05
10	0.03	0.05	more than 0.05
11	0.03	0.04	more than 0.05
12	0.03	0.05	more than 0.05

*Titrated with an antishoop hemolytic system (2 units of hemolysin and 1 c.c. of a 1 per cent suspension of corpuscles).

Guinea pig complement is somewhat more resistant to heat; Noguchi and Bronfenbrenner⁵ found that the activity of sera heated at 55° C. for thirty minutes was reduced to 1/30 or 1/40 the original strength of unheated serum, but was not completely destroyed. In our experiments activity was reduced at least tenfold when sera were

TABLE III

INFLUENCE UPON HUMAN COMPLEMENT OF HEATING AT VARYING TEMPERATURES
IN A WATER-BATH FOR THIRTY MINUTES

SERA	UNITS OF COMPLEMENT*				
	37°C.	40°C.	45°C.	50°C.	55°C.
1	0.03	0.05	more than 0.05	more than 0.05	more than 0.05
2	0.03	0.04	more than 0.05	more than 0.05	more than 0.05
3	0.03	0.03	0.04	more than 0.05	more than 0.05
4	0.04	0.05	more than 0.05	more than 0.05	more than 0.05
5	0.03	0.04	0.05	more than 0.05	more than 0.05
6	0.03	0.04	0.05	more than 0.05	more than 0.05

*Titrated with an antisheep hemolytic system (2 units of hemolysin and 1 c.c. of a 1 per cent suspension of corpuscles).

TABLE IV

THE INFLUENCE OF HEAT UPON GUINEA PIG COMPLEMENT

SERA	HEAT	UNITS OF COMPLEMENT WITH SERA UNHEATED AND HEATED FOR:						
		UN- HEATED	1 MIN.	3 MIN.	5 MIN.	10 MIN.	15 MIN.	30 MIN.
1	55 C.	0.01	0.01	0.05	0.09	more than 0.1	more than 0.1	more than 0.1
1	50 C.	0.01	0.03	0.03	0.03	0.03	0.03	0.03
2	55 C.	0.01	0.02	0.04	0.09	more than 0.1	more than 0.1	more than 0.1
2	50 C.	0.01	0.02	0.02	0.03	0.03	0.03	0.03

TABLE V

THE INFLUENCE OF HEATING GUINEA PIG COMPLEMENT AT 56° C. IN A WATER-BATH

SERA	UNITS OF COMPLEMENT*				
	Before	1 min.	5 min.	10 min.	15 min.
1	0.03	0.04	0.1	more than 0.1	more than 0.1
2	0.03	0.05	0.1	more than 0.1	more than 0.1
3	0.02	0.03	more than 0.1	more than 0.1	more than 0.1
4	0.02	0.04	0.1	more than 0.1	more than 0.1
5	0.02	0.03	more than 0.1	more than 0.1	more than 0.1

*Titrated with an antisheep hemolytic system (2 units of hemolysin and 1 c.c. of a 2.5 per cent suspension of corpuscles).

TABLE VI

INFLUENCE UPON GUINEA PIG SERUM COMPLEMENT OF HEATING AT VARYING TEMPERATURES IN A WATER-BATH FOR THIRTY MINUTES

SERA	UNITS OF COMPLEMENT*				
	37°C.	40°C.	45°C.	50°C.	55°C.
1	0.03	0.04	0.04	more than 0.05	more than 0.05
2	0.02	0.02	0.02	more than 0.05	more than 0.05
3	0.03	0.03	0.05	more than 0.05	more than 0.05
4	0.03	0.04	0.05	more than 0.05	more than 0.05
5	0.03	0.03	0.05	more than 0.05	more than 0.05

*Titrated with an antisheep hemolytic system (2 units of hemolysin and 1. c.c. of a 2.5 per cent suspension of corpuscles).

heated at 55° C. for ten minutes (Table IV) ; at 56° C. inactivation began after an exposure of one minute, being one-third reduced in five minutes from which period inactivation was very rapid (Table V). As shown in Table VI inactivation may begin even at 40° C. but does not become marked until the sera are heated at 50°-55° C.

Insofar as destruction of hemolytic complements in fresh undiluted human sera are concerned to a sufficient degree for complement-fixation tests, it would appear that heating the sera at 55° C. in a water-bath for five to ten minutes is sufficient; 50° C. is insufficient. Simon⁶ has recently advocated heating human sera at 55° C. for ten minutes for the purpose of inactivation and we agree with him that this exposure is ample, although it may be insufficient for the removal of the antilysins.

Part 2

INFLUENCE OF HEAT UPON ANTICOMPLEMENTARY SUBSTANCES IN HUMAN SERA

The development of anticomplementary substances (antilysins) in human sera are of great importance in relation to complement-fixation tests, and very probably sera are routinely heated for the Wassermann test more for the purpose of removing these than for the inactivation of complement or destruction of the substance causing proteotropic reactions.

These antilysins appear to inhibit hemolysis by a direct effect upon complement and hence are designated as anticomplementary substances; some are destroyed or rendered inactive by heating the sera

at 54-56° C. for thirty minutes and are designated as thermolabile; others resist this temperature and are designated as thermostabile.

These antilysins have been especially studied by Noguchi⁷, Zinsser and Johnson⁸ and Kyutoku⁹; in the investigation of Kyutoku, sterile sera were found to develop thermolabile antilysins, the rapidity of development depending upon the temperature at which the sera were kept, being three to seven days at room temperature and weeks at lower temperatures (0°-2° C.) Sera contaminated with bacteria and especially staphylococci, rapidly developed thermostabile antilysins, as previously shown by Craig¹⁰; also sera very deeply discolored with hemoglobin due to too long contact of serum and corpuscles. These antilysins were found closely allied with the protein constituents of human sera and especially the globulin fraction; absorption with corpuscles, kaolin, charcoal, etc., removed only a portion whereas filtration of diluted sera through new, chemically clean and sterile Kitasato filters removed all of the antilysins with practically no influence upon the antibody concerned in the Wassermann reaction.

As shown by Kyutoku the antilysins in human sera are but slightly influenced by heating at 40°-50° C.; temperatures between 55° and 62° C. have most effect, although thermostabile antilysins may resist even higher temperatures. Indeed it would appear useless to attempt the removal of thermostabile antilysins from contaminated sera by heating, filtration being the only effective method known at present, but not a practical procedure except for the examination of the special or occasional serum.

Fortunately the great majority of sera collected with ordinary care, kept in an ordinary refrigerator and tested within five days do not become anticomplementary at all or develop antilysins readily removed by heating the sera. In this connection we may state that *sera left with the coagulum for this period of time are apt to be more satisfactory than sera removed from the clot and kept separated for several days.* The important matter, of practical importance insofar as the majority of complement-fixation tests are concerned, is to determine the minimum amount of time for heating sera at 55° C. to remove the thermolabile antilysins.

As shown in Table VII, the antilysins of human sera are not appreciably influenced by heating the sera at 50° C. or less for periods of thirty minutes; at 55° C., however, many of the antilysins are destroyed.

TABLE VII
THE INFLUENCE OF HEAT UPON ANTICOMPLEMENTARY SUBSTANCES IN HUMAN SERUM

SERA	UNHEATED			45° C. for 30 min.			50° C. for 30 min.			55° C. for 30 min.		
	0.01	0.05	0.1	0.01	0.05	0.1	0.01	0.05	0.1	0.01	0.05	0.1
	0.2			0.2			0.2			0.2		
1	++++*	++++	-	++++	++++	-	++++	++	+++	-	-	+
2	++++	++++	-	++++	++++	+	++++	++++	++++	-	-	-
3	++++	++++	-	++++	++++	+	++++	++++	++++	-	-	-
4	++++	++++	++++	++++	++++	++++	++++	++++	++++	+++	+++	+++

*++++ = strong inhibition of hemolysis; +++ = moderate inhibition of hemolysis; ++ = weak inhibition of hemolysis; + = very weak inhibition; - = complete hemolysis.

TABLE VIII
THE INFLUENCE OF HEAT UPON ANTICOMPLEMENTARY SUBSTANCES IN HUMAN SERUM.*

SERA	UNHEATED			55° C. 5 MIN.			55° C. 10 MIN.			55° C. 15 MIN.			55° C. 20 MIN.			55° C. 30 MIN.		
	0.01	0.05	0.1	0.01	0.05	0.1	0.01	0.05	0.1	0.01	0.05	0.1	0.01	0.05	0.1	0.01	0.05	0.1
	0.2			0.2			0.2			0.2			0.2			0.2		
1	++++*	++++	-	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-
2	++++	++++	-	-	+	+	-	-	+	-	-	-	-	-	-	-	-	-
3	++++	++++	-	-	+	+	-	-	+	-	-	-	-	-	-	-	-	-
4	++++	++++	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

*Tests conducted with 2 units of complement; antiseep system.

++++ = strong inhibition of hemolysis; +++ = moderate inhibition of hemolysis; ++ = weak inhibition of hemolysis; + = very weak inhibition, - = complete hemolysis.

As shown in Table VIII, heating sera at 55° C. for five minutes may result in a marked reduction of the antilysins, the effects becoming more marked as heating is continued; after fifteen minutes of heating the thermolabile antilysins in the majority of sera are destroyed. Tests with a large number of sera varying in age from one to ten days kept at 6-8° C. and used in amounts of 0.1 c.c. unheated and after heating at 55° C. for 1, 5, 10, 15, 20 and 30 minutes, have shown that *the antilysins of over 90 per cent of ordinary sera, that is, clear and containing not more than traces of hemoglobin but sometimes showing the presence of bacteria in cultures, are effectually removed by heating at 55° C. for 15 minutes.* For ordinary work this exposure is sufficient; occasionally sera prove anticomplementary after this amount of heating, but most of these contain thermostable antilysins which effectually resist higher temperatures and more prolonged exposures and particularly heating at 54°-56° C. for thirty minutes, as is the usual custom.

Cerebrospinal fluid seldom develops antilysins unless contaminated with bacteria; unlike sterile serum thermolabile antilysins are only exceptionally encountered and in our experience only in fluids containing relatively large amount of protein, as that from paretics. When bacteria are permitted to grow in a fluid both thermolabile and thermostable antilysins may develop but under ordinary circumstances *cerebrospinal fluid may be used unheated; when heating is required 55° C. for 15 minutes is usually sufficient for the removal of thermolabile antilysins.*

Part 3

THE INFLUENCE OF HEAT UPON PROTEOTROPIC COMPLEMENT-FIXATION

In this part of our investigation only the sera of persons known to be healthy and nonsyphilitic were employed; for these reasons our supply was limited to a circle of physicians and laboratory assistants, as the statements of dispensary and hospital patients were not considered sufficiently safe and certain. A small percentage of these sera yielded weakly positive complement-fixation reactions with a variety of antigens including cholesterolized alcoholic extracts of heart muscle, plain alcoholic extracts of heart muscle, alcoholic extracts of syphilitic liver and acetone insoluble lipoids of beef heart.

In our experience a serum found to yield this reaction with any one antigen was apt to do so with all although the reactions were usually stronger with the cholesterolized extracts; the results shown

TABLE IX
THE INFLUENCE OF HEAT UPON PROTEOTROPIC COMPLEMENT FIXATION WITH THE SERA OF THREE
HEALTHY NONSYPHILITIC PERSONS.*

SERA	UNHEATED						55° C. FOR 15 MINUTES			55° C. FOR 30 MINUTES		
	0.1		0.025		0.006		0.0015		0.0004		C	
	+	+	+	+	+	+	+	+	+	+	+	+
1	+	+	+	+	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	+	+	+	+	+
3	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++

*Results observed with an extract of acetone insoluble lipoids; antishoop system.

in Table IX were observed with the sera of three laboratory assistants believed free of syphilis as surely as this can be established, and an excellent extract of acetone insoluble lipoids of beef heart prepared as described by Noguchi; serum No. 3 gave a particularly strong reaction for proteotropic complement fixation. As shown in this table the substance responsible for these reaction was removed by heating the sera at 55° C. for 15 minutes.

As shown in Table X the destruction of this nonspecific substance in unheated serum begins when serum is heated at 45-50° C. for thirty minutes and is usually completely destroyed when serum is heated at 50° C. for this period of time; at 55° C. destruction begins after serum is heated for one minute and is usually complete after five minutes (Table XI).

In this connection the presence of natural antisheep hemolysin in human sera is of importance; as shown in Tables IX and X the largest amount of serum employed in the tests (0.1 c.c.) gave no proteotropic fixation of complement because of an excess of hemolysin; when heating was begun (Table IX) natural hemolysin decreased with an increase in the degree of proteotropic fixation, until a temperature was reached (50-55° C.) at which the substance in serum responsible for proteotrope fixation was destroyed.

TABLE X
THE INFLUENCE OF HEAT UPON PROTEOTROPIC COMPLEMENT FIXATION*

SERUM	RESULTS					
	0.1	0.025	0.006	0.0015	0.0004	CONTROL
Unheated	-	++	+	-	-	-
40°C. 30 min.	-	+++	++	+	-	-
45°C. 30 min.	-	+++	+	-	-	-
50°C. 30 min.	-	-	-	-	-	-
55°C. 30 min.	-	-	-	-	-	-

*Tests conducted with an extract of acetone insoluble lipoids; antisheep system.

TABLE XI
THE INFLUENCE OF HEAT UPON PROTEOTROPIC COMPLEMENT FIXATION*

SERUM	RESULTS					
	0.1	0.025	0.006	0.0015	0.0004	Control
Unheated	-	++	+	-	-	-
55°C. 1 min.	-	+	+	-	-	-
55°C. 5 min.	-	-	-	-	-	-
55°C. 10 min.	-	-	-	-	-	-
55°C. 15 min.	-	-	-	-	-	-
55°C. 20 min.	-	-	-	-	-	-
55°C. 30 min.	-	-	-	-	-	-

*Tests conducted with an extract of acetone insoluble lipoids; antisheep system.

Many of those serologists employing unheated serum in modifications of the Wassermann test make no mention of the occurrence of these pseudopositive or proteotropic reactions; one of us (Kolmer) found that they may occur with the Hecht-Gradwohl test but only in a small percentage of cases, four per cent being found when crude alcoholic extracts were employed for antigens¹¹ and a much smaller percentage or none at all with extracts of acetone insoluble lipoids¹². Since Seligman and Pinkus² showed that unheated human serum may inhibit the activity of guinea pig complement, which property is abolished by heating human serum for thirty minutes, a large literature on the Noguchi test has shown that many investigators found these proteotropic reactions with unheated serum and in the army laboratories where a modified Noguchi test is employed by Vedder¹³ and Craig,¹⁴ and in naval laboratories by Stitt and Clark,¹⁵ all sera are heated at 54-56° C. for thirty minutes. Thomsen and Boas¹⁶ have also called attention to the fact that falsely positive reactions may occur with unheated serum from nonsyphilitic patients with cancer, nephritis, scarlet fever, leprosy and tuberculosis, but with heated sera positive reactions occur only with syphilitic sera. According to these authors heating sifts out all but the true syphilitic cases, syphilitic serum being the only thermoresisting one. This latter statement, however, cannot be accepted inasmuch as abundant evidence indicates that the heated serum in yaws and leprosy may also yield positive Wassermann reactions. Graetz¹⁷ denies the occurrence of these pseudopositive reactions with unheated sera and believes that with proper technic it is possible to obtain reliable results.

Undoubtedly the kind of antigen employed bears an important relation to the occurrence of proteotropic reactions and practically all serologists using unheated serum follow Noguchi's advice and employ extracts of acetone insoluble lipoids for antigen, as Gurd,¹⁸ Gradwohl,¹⁹ Kolmer,¹¹ Thompson,²⁰ Bronfenbrenner and Schlesinger,²¹ Seelman,²² Bruce,²³ Butler and Landon²⁴ and Bartlett and O'Shansky;²⁵ in European laboratories crude extracts apparently are employed, as in tests of Hecht,²⁶ Tschernogubow²⁷ and Emery²⁸.

This abundant evidence tends to greatly minimize the importance of proteotropic reactions with unheated serum provided good extracts of acetone insoluble lipoids are employed for antigens, but in our experience the possibility still exists and is always a disturbing factor

in the interpretation of the results of tests with the serum of a person who denies luetic infection, shows no clinical evidences of the disease and yields a positive reaction with unheated serum and a negative reaction with heated serum. *For this reason we believe advisable the heating of sera for the syphilis complement-fixation test making up for the inevitable loss in sensitiveness due to some destruction of syphilis antibody by the use of antigens more delicate than acetone insoluble lipoids and by other technical procedures, for the purpose of removing the substances in human serum responsible for the pseudo positive or proteotropic reaction heating in a water-bath for five minutes at 55° C. is sufficient.*

As far as we can ascertain no one has found unheated cerebrospinal fluid yielding pseudopositive or proteotropic reactions; we have never encountered such fluid from nonsyphilitic persons even when tested in large amounts, as much as 2 c.c. in terms of the original Wassermann test. As previously mentioned, these fluids do not readily become anticomplementary and consequently do not require heating.

Part 4

THE INFLUENCE OF HEATING SYPHILITIC SERUM UPON THE ANTIBODY CONCERNED IN THE WASSERMANN REACTION

The majority of those serologists employing unheated serum in various modifications of the Wassermann reactions have stated that syphilis antibody is partially destroyed when sera are heated at 54-56° C. for thirty minutes, but few have published the results of experiments showing the amount of destruction.

Noguchi³ has shown that the antibody may be completely destroyed by heating serum to 72-80° C. for twenty minutes; at 50° C. the antibody was reduced about one-half and at 55° C. about three-quarters, in syphilitic sera heated for twenty minutes. When sera were heated at 55° C. the antibody was reduced one-third in five minutes and at the end of an hour only one-tenth of the original amount of antibody remained. Sachs²⁹ found that heating syphilitic sera at 62° C. for thirty minutes destroyed the complement-fixing antibody and Marie and Levaditi³⁰ have reported that the antibody in cerebrospinal fluid was destroyed by heating at 75-80° C. for twenty minutes.

In conducting our experiments fresh syphilitic sera were used in decreasing amounts in order to render the tests quantitative for the

detection of slight destruction of antibody; antishoop and antihuman hemolytic systems were employed and in each experiment the same complement and antigen were used in order to render the results strictly comparative.

The results are best shown in the tables; such marked variations were found in the thermoresisting power of the antibody concerned in the Wassermann reaction that graphic charts and summaries do not show the effects of heat as well as the study of individual tables.

The tables show the amount of heating and the results observed with decreasing amounts of each serum; 4 (++++) indicates strongly positive or absolute inhibition of hemolysis; 3 (+++) moderately positive or 75 per cent inhibition of hemolysis; 2 (++) weakly positive or 50 per cent inhibition of hemolysis; 1 (+) very weakly positive or 25 per cent inhibition of hemolysis and (-) indicates complete hemolysis or negative. In all instances the results were read after the corpuscles had settled in order to render the readings as clear and accurate as possible.

Tables XII and XIII and XIV show the influence of heating syphilitic sera in a water-bath for thirty minutes at temperatures varying from 40 to 55° C.; as shown in Tables XII and XIV destruction of antibody began even at 40° C. and became progressively more marked with higher temperatures. The serum used in Table XIV showed no change; this serum yielded unusually strong reactions and the antibody was highly thermostable or heat resisting. As shown in Table XII some of the smaller amounts of unheated serum and serum heated at 40-45° C. gave stronger reactions than the larger amounts; this result was ascribed to the presence and influence of natural antishoop hemolysin, which was partially destroyed after the sera had been heated at 45-55° C.

TABLE XII

THE INFLUENCE OF HEATING SERA FOR THIRTY MINUTES UPON SYPHILIS ANTIBODY*

CONDITION OF SERA	RESULTS WITH VARYING AMOUNTS OF SERUM					
	0.1	0.025	0.006	0.0015	0.0004	C
Unheated	2	4	4	-	-	-
Heated at 40°C.	2	3	1	-	-	-
Heated at 45°C.	2	3	1	-	-	-
Heated at 50°C.	2	2	-	-	-	-
Heated at 55°C.	2	1	-	-	-	-

*Antishoop system; cholesterolized extract.

TABLE XIII

THE INFLUENCE OF HEATING SERA FOR THIRTY MINUTES UPON SYPHILIS ANTIBODY*

CONDITION OF SERA	RESULTS WITH VARYING AMOUNTS OF SERUM					
	0.1	0.025	0.006	0.0015	0.0004	C
Unheated	4	4	4	4	4	-
Heated at 40°C.	4	4	4	4	4	-
Heated at 45°C.	4	4	4	4	4	-
Heated at 50°C.	4	4	4	4	4	2
Heated at 55°C.	4	4	4	4	4	-

*Antisheep system; cholesterolized extract.

TABLE XIV

THE INFLUENCE OF HEATING SERA FOR THIRTY MINUTES UPON SYPHILIS ANTIBODY*

CONDITION OF SERA	RESULTS WITH VARYING AMOUNTS OF SERUM					
	0.1	0.025	0.006	0.0015	0.0004	C
Unheated	4	4	4	4	1	-
Heated at 40°C.	4	4	4	3	-	-
Heated at 45°C.	4	4	4	3	-	-
Heated at 50°C.	4	4	4	1	-	-
Heated at 55°C.	4	4	3	-	-	-

*Antisheep system; cholesterolized extract.

Tables XV, XVI, and XVII show the rapidity of destruction of syphilis antibody in these same sera heated in a water-bath at 55° C. for five to sixty minutes; at this temperature there is a considerable loss of antibody within five minutes and after fifteen minutes slightly greater destruction. From fifteen minutes to one hour there is comparatively much less destruction of antibody. It is worthy of special note that these changes were brought out only by using small amounts of serum and that tests using single large amounts may show no changes at all.

TABLE XV

THE EFFECT OF HEATING SERA AT 55°C. UPON SYPHILIS ANTIBODY*

CONDITION OF SERA	RESULTS WITH VARYING AMOUNTS OF SERUM					
	0.1	0.025	0.006	0.0015	0.0004	CONTROL
Unheated	2	4	4	-	-	-
Heated 5 minutes	2	2	-	-	-	-
Heated 10 minutes	2	1	-	-	-	-
Heated 15 minutes	2	1	-	-	-	-
Heated 20 minutes	2	1	-	-	-	-
Heated 30 minutes	2	1	-	-	-	-
Heated 45 minutes	2	1	-	-	-	-
Heated 60 minutes	2	1	-	-	-	-

*Antisheep system; cholesterolized extract.

TABLE XVI

THE EFFECT OF HEATING SERA AT 55°C. UPON SYPHILIS ANTIBODY*

CONDITION OF SERA	RESULTS WITH VARYING AMOUNTS OF SERUM					
	0.1	0.025	0.006	0.0015	0.0004	Control
Unheated	4	4	4	4	4	—
Heated 5 minutes	4	4	4	4	4	—
Heated 10 minutes	4	4	4	4	4	—
Heated 15 minutes	4	4	4	4	4	—
Heated 20 minutes	4	4	4	4	4	—
Heated 30 minutes	4	4	4	4	4	—
Heated 45 minutes	4	4	4	4	4	—
Heated 60 minutes	4	4	4	4	4	—

*Antisheep system; cholesterolized extract.

TABLE XVII

THE EFFECT OF HEATING SERA AT 55°C. UPON SYPHILIS ANTIBODY*

CONDITION OF SERA	RESULTS WITH VARYING AMOUNTS OF SERUM					
	0.1	0.025	0.006	0.0015	0.0004	Control
Unheated	4	4	4	4	1	—
Heated 5 minutes	4	4	4	3	—	—
Heated 10 minutes	4	4	4	1	—	—
Heated 15 minutes	4	4	3	—	—	—
Heated 20 minutes	4	4	3	—	—	—
Heated 30 minutes	4	4	3	—	—	—
Heated 45 minutes	4	4	3	—	—	—
Heated 60 minutes	4	4	3	—	—	—

*Antisheep system; cholesterolized extract.

Tables XVIII, XIX, XX and XXI show the reactions with fifty-one syphilitic sera tested unheated and after heating at 55° C. for varying periods of time with an antisheep hemolytic system and a cholesterolized alcoholic extract of heart muscle for antigen; practically every serum showed most loss of antibody during the first fifteen minutes of heating, with somewhat greater losses after thirty minutes and still more at the end of one hour.

Table XXII gives the reactions observed with twelve syphilitic sera tested unheated and after heating at 55 to 62° C. for intervals varying from fifteen minutes to one hour with an antihuman hemolytic system and an extract of acetone insoluble lipoids for antigen; many of these sera proved slightly anticomplementary when used unheated which added to the degrees of complement fixation. After heating for fifteen minutes at 55° C. some loss of antibody occurred with still greater loss after heating for thirty minutes, especially evident with serum No. 2. A great loss of antibody occurs when sera

TABLE XVIII
THE INFLUENCE OF HEAT UPON SYPHILITIC ANTIBODY*

SERA	UNHEATED					56° C. FOR 15 MINUTES					56° C. FOR 30 MINUTES					56° C. FOR 1 HOUR				
	0.0001	0.001	0.01	0.1	Control	0.0001	0.001	0.01	0.1	Control	0.0001	0.001	0.01	0.1	Control	0.0001	0.001	0.01	0.1	Control
1	1	2	4	4	-	1	4	4	4	-	-	4	4	4	-	-	-	4	4	-
2	2	4	4	4	1	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
3	1	3	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
4	2	4	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
5	-	4	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
6	1	4	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
7	2	3	4	4	-	1	4	4	4	-	1	4	4	4	-	-	-	4	4	-
8	1	4	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
9	-	1	3	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
10	-	2	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
11	-	1	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
12	-	1	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
13	3	3	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
14	3	3	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
15	-	1	3	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
16	1	2	3	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
17	-	2	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
18	-	1	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
19	3	4	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
20	-	2	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
21	1	3	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
22	-	1	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
23	-	1	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
24	-	1	4	4	-	-	4	4	4	-	-	4	4	4	-	-	-	4	4	-
25	3	4	4	4	-	2	4	4	4	-	1	4	4	4	-	4	4	4	4	-

*Tests conducted with antileop hemolytic system using one-half Wassermann amounts and cholesterolized extract.

TABLE XIX
THE INFLUENCE OF HEAT UPON SYPHILITIC ANTIBODY*

SERA	UNHEATED					56° C. FOR 30 MINUTES					56° C. FOR 1 HOUR				
	0.025	0.05	0.1	0.2	C	0.025	0.05	0.1	0.2	C	0.025	0.05	0.1	0.2	C
1	-	4	4	4	-	-	3	4	4	-	-	3	4	4	-
2	-	4	4	4	-	-	4	4	4	-	-	4	4	4	-
3	1	4	4	4	-	-	3	4	4	-	-	2	4	4	-
4	-	3	4	4	1	-	1	3	3	-	-	1	3	3	-
5	-	1	2	2	-	-	1	2	3	-	-	1	3	3	-
6	4	4	4	4	-	1	4	4	4	-	-	4	4	4	-

*Tests conducted with antiseep system and cholesterolized extract.

TABLE XX
THE INFLUENCE OF HEAT UPON SYPHILIS ANTIBODY*

SERA	UNHEATED					HEATED 55° C. 15 MINUTES					HEATED 55° C. 30 MINUTES				
	0.025	0.05	0.06	0.0015	0.0004	C	0.1	0.25	0.006	0.0015	0.0004	C	0.1	0.25	0.006
1	4	4	4	2	-	-	2	2	1	-	-	-	2	2	1
2	4	4	4	3	-	-	4	4	3	-	-	-	4	4	1
3	4	4	4	2	-	-	4	4	4	1	-	-	4	4	4
4	4	4	4	1	-	-	4	4	4	-	-	-	4	4	1
5	4	4	4	-	-	-	4	4	1	-	-	-	4	4	-
6	4	4	4	4	2	-	4	4	4	1	-	-	4	4	1
7	4	4	4	4	-	-	4	4	4	-	-	-	4	4	-
8	4	4	3	-	-	-	4	4	1	-	-	-	4	4	-

*Tests conducted with antiseep system and acetone insoluble lipoids.

TABLE XXI
THE INFLUENCE OF HEAT UPON SYPHILIS ANTIRODY IN HEMOLYSIN FREE SERA*

SERA	UNHEATED				56° C. FOR 10 MIN.				56° C. FOR 20 MIN.				56° C. FOR 30 MIN.				56° C. FOR 45 MIN.				56° C. FOR 60 MIN.			
	Control				Control				Control				Control				Control				Control			
	0.005	0.02	0.1	Control	0.005	0.02	0.1	Control	0.005	0.02	0.1	Control	0.005	0.02	0.1	Control	0.005	0.02	0.1	Control	0.005	0.02	0.1	Control
1	4	4	4	3	3	4	4	-	3	4	4	-	3	4	4	-	3	4	4	-	3	3	3	-
2	3	4	4	2	3	4	4	1	3	4	4	1	3	4	4	1	3	4	4	1	3	2	4	-
3	3	4	4	2	3	4	4	-	3	4	4	-	3	4	4	-	3	4	4	-	3	2	4	-
4	4	4	4	1	4	4	4	1	4	4	4	1	4	4	4	1	4	4	4	1	4	4	4	-
5	4	4	4	1	4	4	4	-	4	4	4	-	4	4	4	-	4	4	4	-	4	4	4	-
6	4	4	4	1	4	4	4	-	4	4	4	-	4	4	4	-	4	4	4	-	4	4	4	-
7	-	3	3	-	-	3	3	-	-	3	3	-	-	3	3	-	-	3	3	-	-	3	3	-
8	4	4	4	-	4	4	4	-	4	4	4	-	4	4	4	-	4	4	4	-	4	4	4	-
9	4	4	4	-	4	4	4	-	4	4	4	-	4	4	4	-	4	4	4	-	4	4	4	-
10	-	3	3	-	-	3	3	-	-	3	3	-	-	3	3	-	-	3	3	-	-	3	3	-
11	4	4	4	-	4	4	4	-	4	4	4	-	4	4	4	-	4	4	4	-	4	4	4	-
12	4	4	4	-	4	4	4	-	3	4	4	-	3	4	4	-	3	4	4	-	3	4	4	-

*Tests conducted with antiaheep system and cholesterolized extract.

TABLE XXII
THE INFLUENCE OF HEAT UPON SYPHILIS ANTIBODY.

SERA	UNHEATED			56 C. FOR 15 MIN.			56 C. FOR 30 MIN.			56 C. FOR 1 HOUR			62 C. FOR 30 MIN.			62 C. FOR 1 HOUR				
	0.1	0.01	0.001	Control	0.1	0.01	0.001	Control	0.1	0.01	0.001	Control	0.1	0.01	0.001	Control	0.1	0.01	0.001	Control
1	4	4	4	2	4	4	4	1	4	4	4	1	4	4	4	1	4	4	4	1
2	4	4	4	2	4	4	4	1	4	4	4	1	4	4	4	1	4	4	4	1
3	4	4	4	1	4	3	4	1	4	1	4	1	4	1	4	1	4	1	4	1
4	4	4	4	1	4	4	4	1	4	4	4	1	4	4	4	1	4	4	4	1
5	4	4	4	4	4	4	4	1	4	4	4	1	4	4	4	1	4	4	4	1
6	4	4	4	4	4	4	4	1	4	4	4	1	4	4	4	1	4	4	4	1
7	4	4	4	1	4	3	3	1	4	4	4	1	4	4	4	1	4	4	4	1
8	4	4	4	1	4	3	3	1	4	4	4	1	4	4	4	1	4	4	4	1
9	4	4	4	1	4	3	3	1	4	4	4	1	4	4	4	1	4	4	4	1
10	4	4	4	1	4	3	3	1	4	4	4	1	4	4	4	1	4	4	4	1
11	4	4	4	1	4	3	3	1	4	4	4	1	4	4	4	1	4	4	4	1
12	4	4	4	1	4	3	3	1	4	4	4	1	4	4	4	1	4	4	4	1

*Tests conducted with an antihuman system and acetone insoluble lipoids.

are heated at 62° C. for thirty minutes, every serum showing the effects with a total loss of antibody in about 35 per cent of sera; when heated at 62° C. for one hour about 60 per cent of sera show complete destruction of antibody.

Tables XXIII, XXIV, XXV, and XXVI show the effects upon syphilis antibody of heating diluted sera and what may be expected when weakly syphilitic sera are heated prior to the conduct of complement-fixation tests; under these circumstances the Wassermann test may fail to detect the presence of antibody because of destruction of the latter during the heating of serum and especially at 55° C. for half an hour. The marked destruction of antibody in sera heated at 62° C. is well shown in the results of these experiments.

While cerebrospinal fluids are not usually heated for the complement-fixation test, they serve well in experiments designed to ascertain the influence of heat upon syphilis antibody and especially since they are usually free of natural hemolysins, and when examined fresh are free of anticomplementary activity; the results of tests with seven fresh fluids from cases of paresis and tabes dorsalis are shown in Table XVII. The loss of antibody as a result of heating at 56° C. for thirty minutes is shown in these tests using varying amounts of each fluid; likewise the great and complete destruction of antibody when fluids are heated at 62° C.

Table XXVIII gives a summary of Wassermann tests with one hundred seventy syphilitic sera; these tests were conducted by the original Wassermann technic except that one-half quantities and a cholesterolized extract were used. Each unheated serum reacted positively; after heating at 56° C. for fifteen minutes 2 per cent sera reacted negatively; after heating at 56° C. for thirty minutes, 5 per cent reacted negatively; after heating at 56° C. for one hour, 8 per cent reacted negatively and after 62° C. for thirty minutes, 60 per cent reacted negatively, showing the profound influence of this amount of heat upon the antibody concerned in the Wassermann reaction. These changes are plotted in the form of a curve shown in Chart 1, as likewise a curve showing the percentage of weaker positive reactions consequent to heating the sera. The greatest drop occurred within the first fifteen minutes of heating at 56° C., about 20 per cent of sera showing weaker positive reactions than observed with unheated sera.

TABLE XXIII
THE INFLUENCE OF HEAT UPON SYPHILIS ANTIBODY IN DILUTED SERUM*

DILU- TIONS	UNHEATED					HEATED 56°C. FOR 30 MINUTES					HEATED 62°C. FOR 1 HOUR							
	0.2	0.4	0.6	0.8	1.0	C	0.2	0.4	0.6	0.8	1.0	C	0.2	0.4	0.6	0.8	1.0	C
1:10	4	4	4	4	4	-	3	3	4	4	4	-	-	-	1	2	2	-
1:25	2	4	4	4	4	-	-	1	3	4	4	-	-	-	-	-	-	-
1:50	-	1	3	4	4	-	-	-	-	-	1	-	-	-	-	-	-	-
1:100	-	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-

* Antisheep system; cholesterolized extract

*Antisheep system; cholesterolized extract.

TABLE XXIV
THE INFLUENCE OF HEAT UPON SYPHILIS ANTIBODY IN DILUTED SERUM*

DILU- TIONS	UNHEATED					C	HEATED 56° C. FOR 30 MINUTES					C	HEATED 62° C. FOR 1 HOUR					C
	0.2	0.4	0.6	0.8	1.0		0.2	0.4	0.6	0.8	1.0		0.2	0.4	0.6	0.8	1.0	
1:10	3	4	4	4	4	-	2	3	4	4	4	-	-	-	-	-	-	-
1:25	2	4	4	4	4	-	-	-	1	2	3	-	-	-	-	-	-	-
1:50	-	-	1	3	4	-	-	-	-	-	1	-	-	-	-	-	-	-
1:100	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-

*Antisheep system; cholesterolized extract.

TABLE XXV
THE INFLUENCE OF HEAT UPON SYPHILIS ANTIBODY IN DILUTED SERUM*

DILU- TIONS	UNHEATED					HEATED 56° C. FOR 30 MINUTES					HEATED 62° C. FOR 1 HOUR							
	0.2	0.4	0.6	0.8	1.0	C	0.2	0.4	0.6	0.8	1.0	C	0.2	0.4	0.6	0.8	1.0	C
1:10	3	4	4	4	4	-	1	3	4	4	4	-	-	-	-	-	-	-
1:25	-	2	4	4	4	-	-	-	-	-	2	-	-	-	-	-	-	-
1:50	-	-	1	2	3	-	-	-	-	-	1	-	-	-	-	-	-	-
1:100	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

*Antisheep system; cholesterolized extract.

TABLE XXVI
THE INFLUENCE OF HEAT UPON SYPHILIS ANTIBODY IN DILUTED SERUM*

DILU- TIONS	UNHEATED					HEATED 56° C. FOR 30 MINUTES					HEATED 62° C. FOR 1 HOUR							
	0.2	0.4	0.6	0.8	1.0	C	0.2	0.4	0.6	0.8	1.0	C	0.2	0.4	0.6	0.8	1.0	C
1:10	4	4	4	4	4	-	4	4	4	4	4	-	2	3	3	4	4	-
1:25	4	4	4	4	4	-	4	4	4	4	4	-	1	2	2	3	3	-
1:50	4	4	4	4	4	-	4	4	4	4	4	-	-	-	-	-	-	-
1:100	2	4	4	4	4	-	1	4	4	4	4	-	-	-	-	-	-	-

*Antisheep system; cholesterolized extract.

TABLE XXVII
THE INFLUENCE OF HEAT UPON SYPHILIS ANTIBODY IN CEREBROSPINAL FLUID*

SPINAL FLUIDS	UNHEATED						HEATED 56°C. FOR 30 MINUTES						HEATED 62°C. FOR 1 HOUR					
	0.1	0.2	0.4	0.6	0.8	1.0	0.1	0.2	0.4	0.6	0.8	1.0	0.1	0.2	0.4	0.6	0.8	1.0
No. 1	3	4	4	4	4	4	2	4	4	4	4	4	-	-	-	-	1	1
No. 2	1	4	4	4	4	4	-	3	4	4	4	4	-	-	-	1	2	2
No. 3	-	4	4	4	4	4	-	3	4	4	4	4	-	-	-	-	-	-
No. 4	-	-	-	-	1	1	-	-	-	-	1	1	-	-	-	-	1	-
No. 5	-	-	-	2	4	4	-	-	-	1	3	3	-	-	-	-	-	2
No. 6	-	-	-	1	3	4	-	-	-	-	-	-	-	-	-	-	-	-
No. 7	-	-	-	1	4	4	-	-	-	-	3	4	-	-	-	-	-	-

* Antisheep hemolytic system; cholesterolized extract.

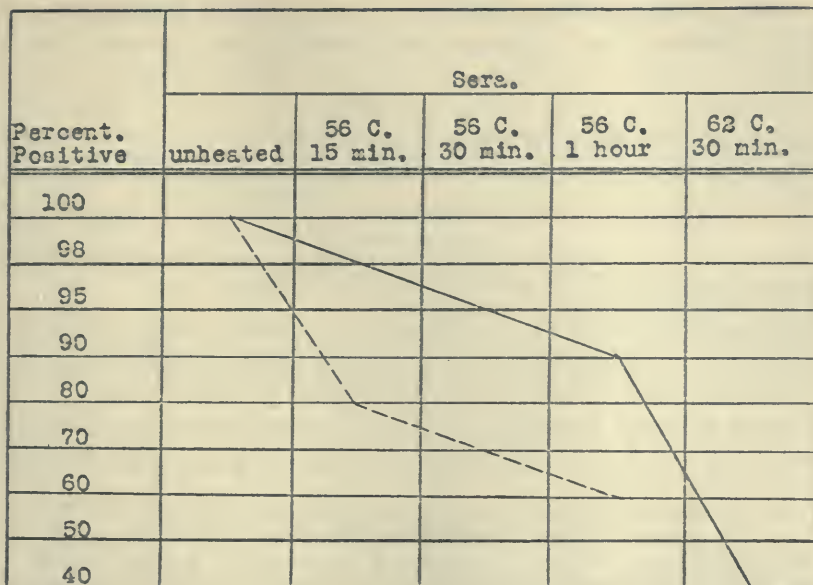


Chart 1. Influence of heat upon syphilis antibody; Wassermann tests with 170 syphilitic sera, each serum being tested in 0.1 c.c.

— = curve showing percentage of positive reactions.

----- = curve showing percentage of weaker positive reactions.

TABLE XXVIII

RESULTS OF COMPLEMENT-FIXATION TESTS WITH 170 SYPHILITIC SERA*

HEATING	REACTIONS AS COMPARED WITH REACTIONS WITH UNHEATED SERA		
	Per cent equal or stronger	Per cent weaker	Per cent negative
56°C. for 15 minutes	80	18	2
56°C. for 30 minutes	64	31	5
56°C. for 1 hour	42	50	8
62°C. for 30 minutes	7	33	60

*Tested in amounts of 0.1 c.c. with cholesterolized extract and an antisheep system; each unheated serum gave a positive reaction.

Table XXIX is a summary of the results observed with seventy syphilitic sera tested before and after heating with three antigens in the Wassermann test employing one-half quantities. As shown in the table, 13 to 20 per cent of these sera yielded stronger reactions with unheated sera, but also worthy of special note is that 8 to 14 per cent reacted more strongly with heated sera. A number of these stronger reactions with heated sera are also included in Table XXVIII; they were apparently due to the destruction or masking of natural ther-

molabile antisheep hemolysin³¹ during the process of heating the sera, which increased the delicacy of the hemolytic system with heated sera.

TABLE XXIX

SUMMARY OF RESULTS OF COMPARATIVE WASSELMANN TESTS WITH SEVENTY SYPHILITIC SERA BEFORE AND AFTER HEATING AT 56° C. FOR THIRTY MINUTES*

ANTIGENS	REACTIONS OF EQUAL DEGREE	STRONGER REAC- TIONS WITH UNHEATED SERUM	STRONGER RE- ACTIONS WITH HEATED SERUM
Cholesterolized heart	74%	18%	8%
Alcoholic syphilitic liver	73%	13%	14%
Aceton insoluble lipoids	71%	20%	9%

*Eighty-five sera were tested but of these fifteen sera proved anticomplementary when unheated and three of these remained anticomplementary after heating.

Each serum tested in amount of 0.2 c.c. with each antigen; antisheep system.

Table XXX is a summary of tests conducted with an antisheep system in which the complement was titrated daily instead of the

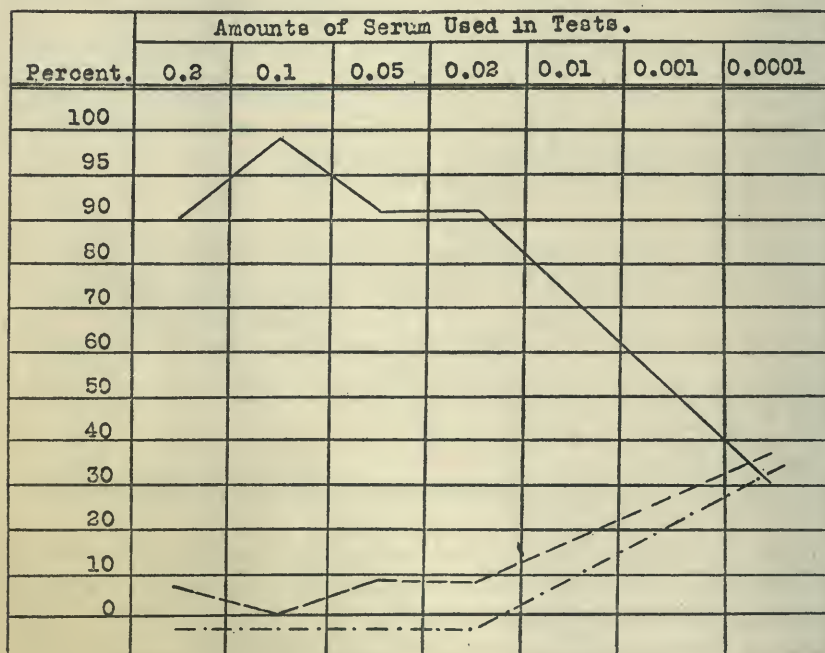


Chart 2. The influence of heating syphilitic sera at 55° C. for 15 minutes.

———— = percentage of sera yielding reactions equal or stronger than observed with unheated sera.
 ----- = percentage of sera yielding reactions weaker than observed with unheated sera.
 - . - . - = percentage of sera yielding falsely negative reactions with heated sera.

hemolysin as in the Wassermann test; each serum was from a luetic individual and tested unheated and again after heating at 55° C. for fifteen, thirty and sixty minutes and at 62° C. for thirty minutes. Only those sera are included which were free of anticomplementary activity. All tests were conducted with a cholesterolized extract. In the table the reactions with heated sera have been compared with those observed with unheated sera and listed as giving equal, weaker,

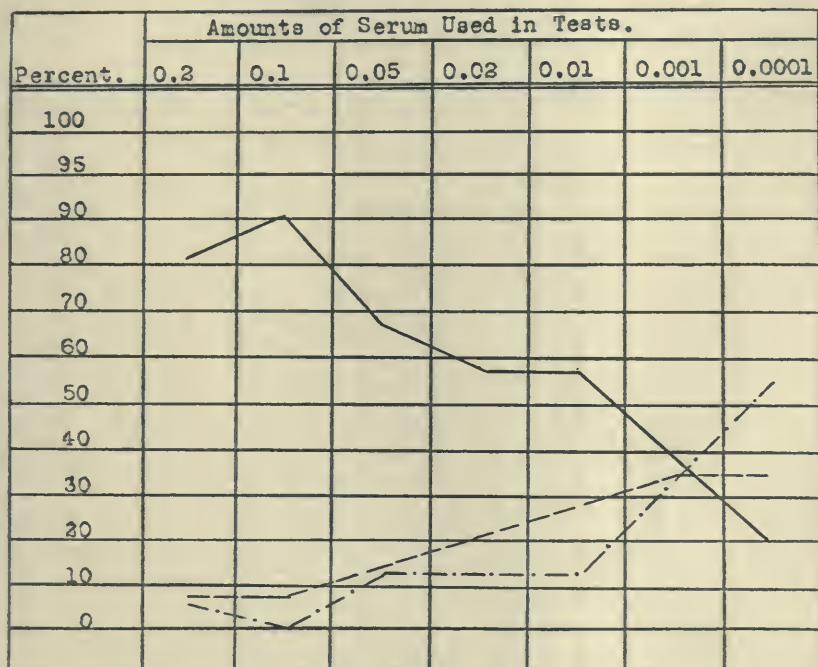


Chart 3. The influence of heating syphilitic sera at 55° C. for 30 minutes.

- = percentage of sera yielding reactions equal or stronger than observed with unheated sera.
 - - - - - = percentage of sera yielding reactions weaker than observed with unheated sera.
 - . - . - . = percentage of sera yielding falsely negative reactions with heated sera.

stronger and falsely negative reactions; charts 2, 3, 4 and 5 show the changes graphically in the form of curves.

After heating the sera at 55° C. for fifteen minutes a small number (less than 10 per cent) were observed to give weaker reactions when tested in amounts from 0.2 to 0.02 c.c., but when smaller amounts were used as 0.01 to 0.0001 c.c. the percentage of weaker reactions

TABLE XXX
SUMMARY OF RESULTS OF COMPLEMENT-FIXATION TESTS INDICATING THE INFLUENCE OF HEATING SERUM UPON SYPHILIS ANTIBODY.

SERA	NUMBER GIV- ING POSITION WITH UN- HEATED SERUM	REACTIONS WITH SERA HEAT- ED AT 55° C. FOR 15 MIN.			REACTIONS WITH SERA HEAT- ED AT 55° C. FOR 30 MIN.			REACTIONS WITH SERA HEAT- ED AT 56° C. FOR 1 HOUR			REACTIONS WITH SERA HEAT- ED AT 62° C. FOR 30 MIN.		
		Equal	Weaker	Negative	Stronger	Equal	Weaker	Negative	Stronger	Equal	Weaker	Negative	Stronger
12 with 0.2 c.c.	12	9	1	1	2	8	1	1	1	2	7	2	1
55 with 0.1 c.c.	55	51	1	1	1	44	5	2	37	16	26	13	1
12 with 0.05 c.c.	12	10	1	1	1	8	2	6	4	1	7	4	1
12 with 0.02 c.c.	12	11	1	1	1	7	4	6	2	1	1	10	1
40 with 0.01 c.c.	37	25	7	3	2	18	12	14	10	1	7	30	1
30 with 0.001 c.c.	29	14	9	6	1	11	10	15	14	1	7	29	1
20 with 0.0001 c.c.	13	4	4	5	1	3	3	7	1	1	1	13	1

increased. No serum yielded a falsely negative reaction until used in amounts from 0.01 to 0.0001 c.c. when the percentage rapidly increased. As shown in Chart 2 tests with 0.1 c.c. serum showed fewer weaker reactions as compared with unheated serum, than tests 0.2 c.c. serum; this result is ascribed to the influence of natural antisheep hemolysin escaping destruction by heating, the amount being greater

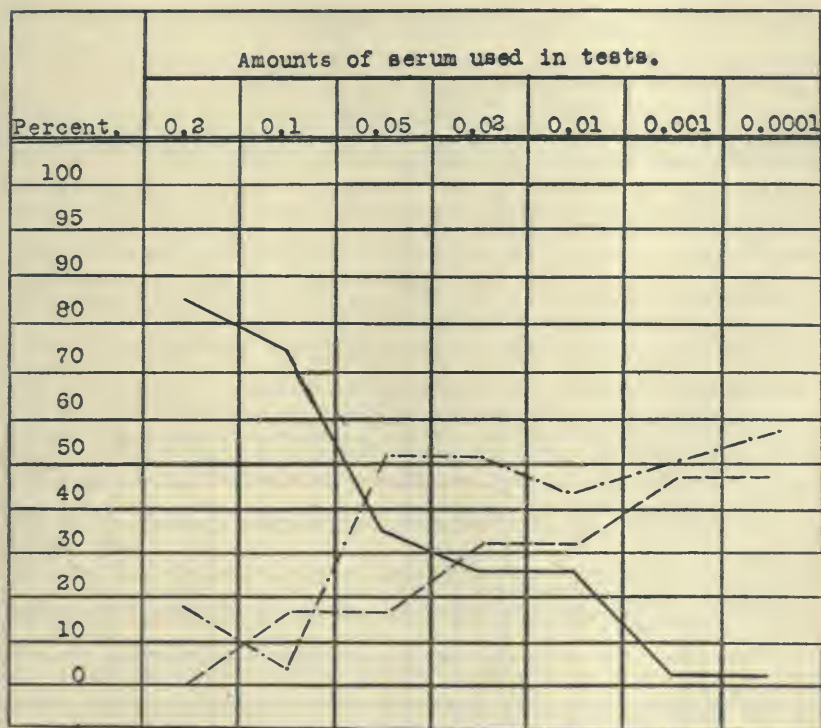


Chart 4. The influence of heating syphilitic sera at 55° C. for one hour.

- = percentage of sera yielding reactions equal or stronger than observed with unheated sera.
- = percentage of sera yielding reactions weaker than observed with unheated sera.
- .-.-.- = percentage of sera yielding falsely negative reactions with heated sera.

in 0.2 c.c. serum than in 0.1 c.c. and the effect upon the hemolytic system correspondingly greater.

After heating the sera at 55° C. for thirty minutes, more marked changes were observed, the percentage of weaker positive reactions being increased and a few being observed to yield apparently falsely

negative reactions (Chart 3); these changes were still more marked with sera heated at 55° C. for one hour (Chart 4) and became extreme with sera heated at 62° C. for thirty minutes (Chart 5).

SUMMARY

1. Complement-fixation tests with unheated sera in which guinea pig complement is used, are sometimes unsatisfactory because of the

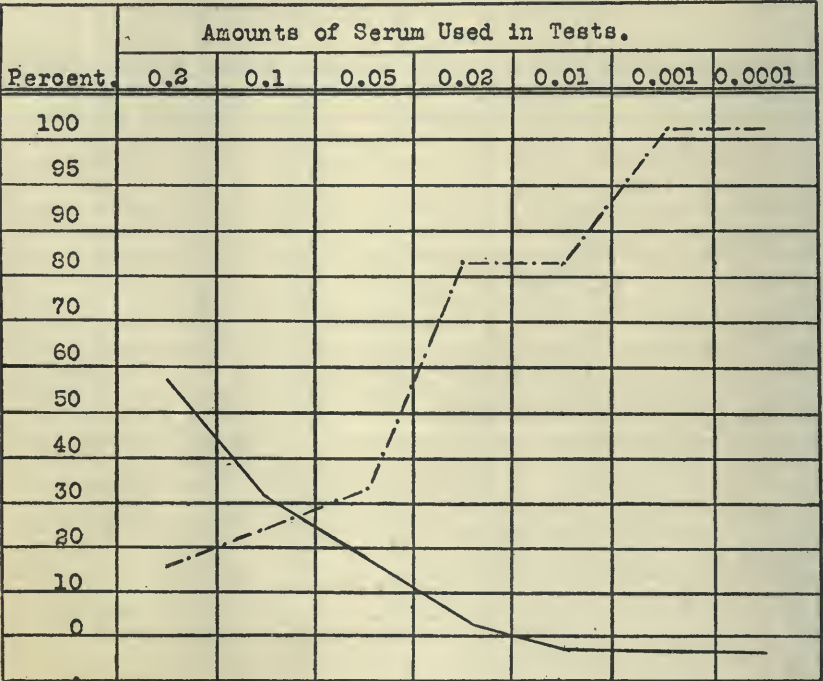


Chart 5. The influence of heating syphilitic sera at 62° C. for 30 minutes.
———— = percentage of sera yielding reactions equal to those observed with unheated sera.
- . - . - = percentage of sera yielding falsely negative reactions with heated sera.

presence of anticomplementary substances (antilynsins) in certain sera; these may be largely avoided by using perfectly fresh sera, but in routine work this practice may not always be possible. The tests with unheated sera are also subject to the error of pseudopositive or proteotropic reactions.

2. Complement-fixation tests with unheated sera in which the

complement of each serum is utilized or both the complement and a natural hemolysin, are open to the objections of requiring fresh sera. the possibility of proteotropic reactions, the possibility of falsely negative reactions due to the lack of fixability of an individual complement, the absence of sufficient complement or hemolysin or both in 2 to 10 per cent of sera and the impossibility of examining spinal fluids.

3. Complement-fixation tests with unheated sera possess, however, the advantage of greater sensitiveness because of the presence of thermolabile and thermostabile syphilis antibody; these tests are likewise usually simpler and more economical of materials and time.

4. Human complement is very susceptible to heat; at 55° C. the complement is reduced to one-tenth of its original strength in ten minutes and an exposure of fifteen minutes at this temperature is ample for the inactivation of sera.

5. The anticomplementary substances (antilynsins) of human sera are thermolabile and thermostabile; in routine work the antilynsins of human sera are usually of the former variety. For the removal of these antilynsins heating sera at 55° C. for fifteen minutes is usually sufficient and particularly with sera tested within five days of the time of collection of blood; thermostabile antilynsins in old and contaminated sera are not removed by this amount of heating but these sera are to be regarded as unsatisfactory for the complement fixation test.

6. For the removal of the substance from human sera responsible for the pseudopositive or proteotropic reaction, heating at 55° C. for five to ten minutes is sufficient.

7. Unheated spinal fluids are not usually anticomplementary unless contaminated with bacteria; furthermore they apparently do not yield proteotropic reactions. For these reasons they may be used unheated in complement-fixation tests. If antilynsins develop they are usually thermolabile and removable by heating at 55° C. for fifteen minutes; if the fluids are cloudy with bacteria the antilynsins are likely to be thermostabile, rendering the fluids unfit for complement-fixation tests.

8. Heating syphilitic serum reduces its power of absorption or fixation of complement with lipoidal extracts due to the destruction of a portion of the antibody, the removal of antilynsins and possibly to the destruction of the substance concerned in the proteotropic reaction.

9. The antibody in syphilitic serum concerned in the complement-fixation reaction is very susceptible to heat, deterioration occurring when sera are heated at 40° C. for thirty minutes and becoming progressive until at 62° C. and higher temperatures, complete destruction occurs. Very probably the antibody occurs in two kinds namely, thermolabile and thermostabile, inasmuch as heating at 55° C. has none or much less influence upon the fixing power of some sera.

10. When syphilitic sera are heated at 55° C. for fifteen minutes falsely negative complement-fixation reactions may occur with 2 per cent of sera containing small amounts of antibody or with sera tested in very small amounts, namely, 0.01 to 0.0001 c.c.; when heated for thirty minutes a slightly greater destruction of antibody occurs producing about 5 per cent falsely negative reactions and a higher percentage of weaker reactions, as compared with tests employing unheated serum. The greatest amount of destruction of antibody occurs during the first fifteen minutes of heating, but heating for thirty minutes according to the usual custom, results in a still greater and useless destruction of antibody.

11. When complement-fixation tests are conducted with an anti-sheep hemolytic system, the reactions with heated sera may be stronger than with unheated sera, due to the destruction or masking of a portion of the natural antisheep hemolysin in human serum by heat and a consequent closer adjustment of the hemolytic system.

CONCLUSIONS

1. Although heating syphilitic sera results in the destruction of a portion of the antibody concerned in the complement-fixation test, it is advisable to heat all sera for the purpose of inactivating native complement and thereby permitting a closer adjustment of the hemolytic system, destroying any antilysins (anticomplementary substances) that may be present and preventing the occurrence of pseudo-positive or proteotropic reactions with the sera of nonsyphilitic persons.

2. For these purposes heating sera at 55° C. for fifteen minutes is sufficient and preferable to the customary period of thirty minutes, inasmuch as less destruction of antibody occurs.

3. The inevitable reduction in the sensitiveness of complement-fixation tests conducted with heated sera should be compensated for in a standardized technic by certain technical procedures and particularly with reference to the kind and amount of antigen employed and the adjustment of the hemolytic system.

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STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. XIV*

THE INFLUENCE OF TEMPERATURE AND DURATION OF PRIMARY INCUBATION UPON THE HEMOLYTIC ACTIVITY OF COMPLEMENT

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IN COMPLEMENT-FIXATION tests the method of conducting the primary incubation of mixtures of patient's serum, complement, and antigen for the fixation of complement, has considerable influence upon the sensitiveness of the reaction; both the temperature employed and the time allowed are factors of importance.

Since heat generally favors and hastens chemical reactions, the primary incubation is usually conducted at 37° to 38° C., and following Wassermann's practice, one hour is generally allowed; numerous investigators have shown, however, that longer periods at lower temperatures apparently increases the amount of complement fixation and thereby the sensitiveness of the reaction.

Since the necessity for increasing the sensitiveness and specific diagnostic value of the complement-fixation test for syphilis and other infections is generally admitted, the method of conducting the primary incubation is one of much practical importance.

REVIEW OF LITERATURE

Wassermann, Neisser and Bruck originally advocated placing the mixtures of serum, antigen and complement in an air incubator for one hour; later the water-bath came into use and was particularly advocated in this country by Noguchi, an incubation of one-half hour in a water-bath at 37-38° C. being regarded equal to one hour in an air incubator.

In 1909 Liefmann¹ found that precipitation of chicken serum by rabbit antichickens serum and fixation of complement by the precip-

*Investigation aided by funds accruing from the preparation of arsphenamine.

itates, was particularly strong after the mixtures had been kept at 0° C. for two hours. Neufeld and Haendel² in a study of the influence of temperature upon complement fixation, reached the conclusion that bacteriolytic complement was not fixed at 0-3° C. by cholera antigen and anticholera serum but only at 37° C., whereas hemolytic complement was fixed at both temperatures; Sachs and Bolkowska³ also found that complement is readily fixed at low temperatures by mixtures of corpuscles and specific hemolysin.

Satta and Donati⁴ studied the question of the influence of temperature upon complement fixation in syphilis followed by Jacobsthal⁵ who examined 200 sera and found 2 per cent more positive reactions with a primary incubation at 4° C. than 37° C. This report was followed by a more extensive study by Guggenheimer⁶ with 623 sera tested with a primary incubation at 0° C. and 37° C.; of these sera 263 gave positive reactions at 37° C. and 267 at 0° C.; 32 sera reacted more strongly at 37° C. and negatively at 0° C. while 12 gave positive reactions at 0° C. and negative reactions at 37° C. By reason of these paradoxical results Guggenheimer suggested the advisability of testing each serum at both temperatures. Somewhat similar results were published by Altmann and Zimmern⁷ who examined 1902 sera; similar reactions were observed with 1610 sera tested with a primary cold and warm incubation but 76 sera reacted positively with a cold incubation and negatively at 37° C. whereas 45 sera reacted negatively with a cold incubation and positively at 37° C. They also found that 96 sera gave stronger reactions with a cold incubation whereas 75 sera gave stronger reactions at 37° C. Later Altmann⁸ studied the subject in reference to the stage of the disease, reporting that a primary incubation at 37° C. gave a higher percentage of positive reactions with the sera of syphilitics during the primary and secondary stages of the disease whereas with sera from the tertiary and latent cases, stronger reactions occurred at 4° C. Leredde and Rubinstein⁹ then published a short paper stating that best results were being observed with an ice box period of primary incubation; Thomsen and Boas¹⁰ also found better fixation at 16-18° C. than at 37° C., but Muller¹¹ reported best results with warm incubation at 37° C.

In this country the subject was first taken up by MacNeal¹² who tested the sera of 463 persons with a crude alcoholic extract of heart muscle; an ice box incubation of 14 hours at 8-12° C. gave 10.3

per cent more positive reactions than observed with the usual incubation of one hour at 37° C. MacNeal also tested 266 sera for gonococcus complement fixation, finding 36.9 per cent more positive reactions with the ice box method. As a result of these studies MacNeal believed that a period of 14 hours at 8-12° C. was best for syphilis complement fixation and 6 hours for gonococcus fixation. Coca and L'Esperance¹³ found that some sera reacted positively only with ice box incubation of 12 to 18 hours, while others yielded positive reactions only at 37° C.; consequently they advised both methods for testing all sera. Kaliski¹⁴ then made a valuable and practical suggestion of combining both methods by giving a primary incubation of two hours in an ice box followed by a half hour in a thermostat.

Smith and MacNeal^{15, 16, 17, 18} have also shown an apparently important relation of the kind of extract employed as antigen to the subject of the influence of temperature upon complement fixation; results of their investigations may be summarized as follows: (1) The use of cholesterolized antigens in tests with a primary incubation at 8° C. for four hours proved the most sensitive, but were also believed to yield nonspecific reactions at both 37° C. and at 8° C. (2) The simple or plain alcoholic extracts used in tests incubated at 8° C. yielded more sensitive reactions than cholesterolized antigens at 37° C. and gave no nonspecific reactions. (3) The acetone insoluble lipid extracts of Noguchi proved less sensitive than cholesterolized extracts both at 8° C. and 37° C.; they were found less sensitive than plain alcoholic extracts at 8° C. but more sensitive at 37° C. and gave no falsely positive reactions.

Ottenberg¹⁹ also reported that cholesterolized extracts gave a considerable proportion of false positive reactions with the ice box method and believes that simple alcoholic antigens with the ice box method of fixation (8-10° C.) gives by far the most delicate and accurate results. Swift²⁰ is quoted as stating that simple alcoholic extracts incubated in the ice box gave results practically identical with those obtained with cholesterolized antigen in the thermostat.

Dean²¹ has made a particularly excellent study of the influence of temperature on the fixation of complement employing normal serum and homologous antiserum and alcoholic organ extract and serum from a syphilitic patient. His experiments have shown the following: (1) mixtures of antigen and antibody fixes more complement at 0° C. than at 37° C.; (2) the time which elapses before the maximum

fixation of complement occurs in any mixture of antigen and antibody depends on the relative proportions of antigen and antibody; an excess of either retards the action. (3) The maximum fixation is attained more rapidly at 37° C. than at 0° C., but the amount of complement fixed is much greater at 0° C. than at 37° C. (4) Complement fixation is due to the adsorption of euglobulin of guinea pig serum by particles of precipitate and this adsorption is favored by keeping the mixture at a low temperature, explaining the fact that more complement is fixed at 0° C. than at 37° C.

Noguchi²² in a study of the influence of primary incubation at 23° C., 30° C., and 37° C. upon complement fixation with extracts of acetone insoluble lipoids, found that complement fixation occurs most rapidly at 37° C.; thirty minutes at 37° C. was found equal to sixty minutes at 30° C. and two hours at 23° C. irrespective of whether human or guinea pig complement was used. Bronfenbrenner and Schesinger²³ have also found 37° C. best for rapid fixation of complement, one half hour incubation at this temperature being found most efficient. For complete fixation of complement incubation in an ice box for eight to ten hours was found best, but may not be specific because fixation is so complete under these conditions "that even traces of secondary circulating antigens and their corresponding antibodies may cause fixation of complement."

Ruediger^{24, 25} found complement fixation better in an incubator at 37° C. than in an open water-bath at the same temperature; complete fixation of complement was found to take place gradually and better at 10° C. than at 21° C. or 37° C. Incubation at 0.5 to 1° C. gave stronger fixation than at 2, 3, 4, 5, 6, 7, 8, 9, 10 and 37° C.; plain alcoholic extracts gave best fixation at 1° C. and acetone insoluble lipoids at 37° C. Ten hours at 1° C. appeared to best meet all requirements. Larkin, Levy and Fordyce²⁶ also appear to favor the ice box method, and Berghausen²⁷ likewise found ice box fixation for 18 to 20 hours at 0° to 2° C. with simple alcoholic extract of syphilitic organ, to yield better results than one hour warm incubation.

PURPOSES OF INVESTIGATION

An analysis of this literature indicates that the majority of investigators have observed stronger Wassermann reactions when the primary incubation was conducted at a low temperature for several hours than after the usual incubation at 38° C. for one-half to

one hour; this result has been generally ascribed to the greater fixation of complement by the antibody in the serum and the antigen. However, other factors require consideration before this conclusion can be accepted as proved and particularly the (a) influence of temperature upon complement alone and (b) upon the anticomplementary activity of antigen and serum. For example, slightly more deterioration of complement may occur at 10° C. for eighteen hours than at 38° C. for one hour and this would necessarily influence the results in the way of apparently stronger Wassermann reactions; or, the antigen alone and serum alone may exert more anticomplementary effects at 10° C. for eighteen hours than at 38° C. for one hour with similar results. These subjects are of particular importance in view of the observations of Smith and MacNeal, Ottenberg and others, showing that cholesterolized extracts are apt to yield non-specific reactions in cold incubations of several hours duration.

For the purpose of reaching a decision regarding the best method of conducting the primary incubation in the complement-fixation test for syphilis, all of these factors require study and consideration, as likewise the velocity and amount of complement fixation in syphilis at varying temperatures and periods of time; also the question raised by Guggenheimer, Altmann, Coca and others regarding the possibility of the existence of one kind of syphilis antibody fixing complement best at 38° C. and a second at lower temperatures.

Our investigations have attempted to cover all of these factors in order to reach a conclusion on the basis of actual experimentation and experience of what constitutes the best method for conducting the primary incubation in the syphilis complement-fixation test; *in this article are given the results of experiments on the influence of temperature and duration of primary incubation upon the hemolytic activity of guinea pig complement.*

TECHNIC

Mixtures of the sera of several guinea pigs were used as complement in each experiment, the sera being collected and prepared after the technic previously described.²³ An antish sheep hemolytic system was employed.

For determining the influence of varying temperatures and periods of time upon complement, a number of sera were titrated by placing varying amounts in a series of test tubes and adding he-

molysin and corpuscles at once as is the usual practice, and repeating the titrations by keeping the tubes at a certain temperature for a definite interval before adding hemolysin and corpuscles followed by secondary incubation in a water-bath at 38° C. for one hour. The different temperatures and time intervals employed are shown in the accompanying tables and charts.

As a general rule each complement was titrated plain and the titration repeated at the same time in the presence of an antigen; as stated in a previous article, the latter method has been adopted for the titration of complement in a standardized test.²⁹

SUMMARY OF RESULTS

The results of several experiments are shown in Tables I and II and Charts 1 and 2; they may be summarized as follows:

1. The temperatures and periods of time advocated for the primary incubation in the Wassermann test have an important bearing upon the hemolytic activity of complement; when complement is titrated

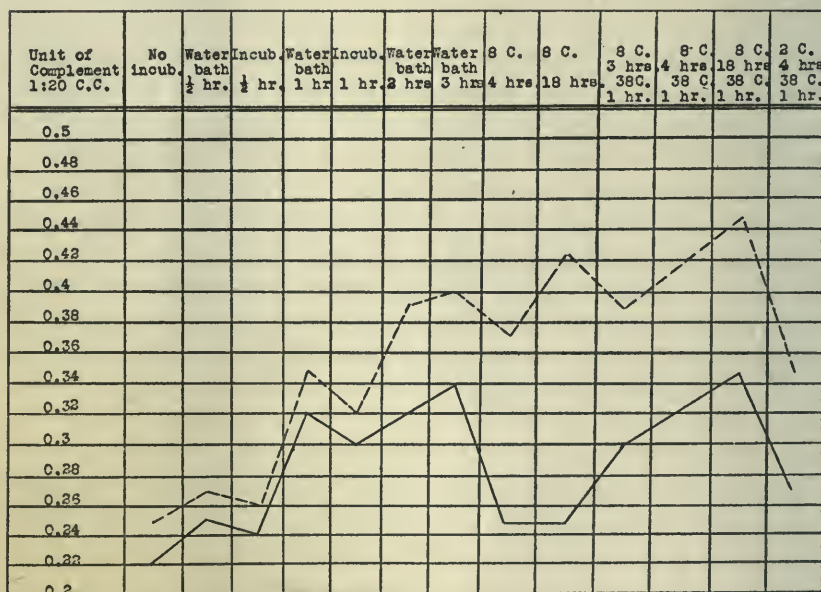


Chart 1. The influence of temperature and duration of primary incubation upon the hemolytic activity of guinea pig complement.

———— = complement titrated plain.

----- = complement titrated in presence of antigen of plain alcoholic extract of beef heart.

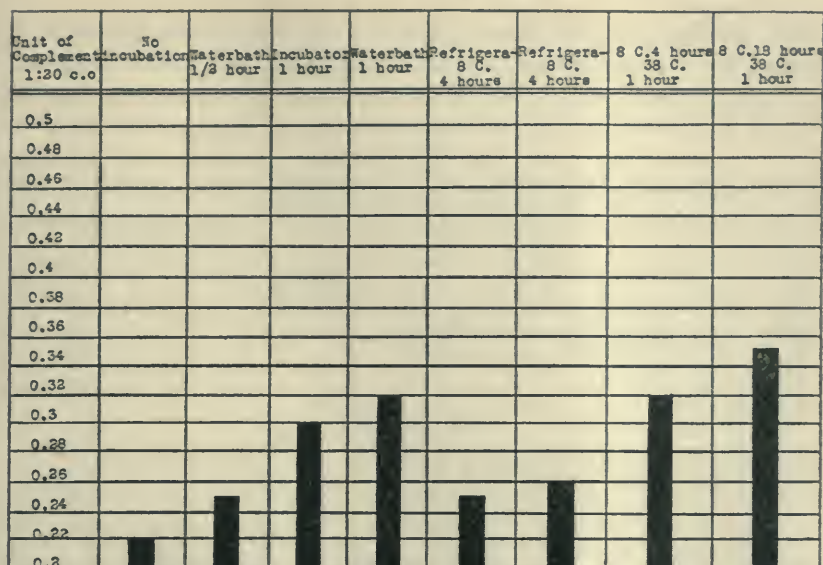


Chart 2. The influence of temperature and duration of primary incubation upon the hemolytic activity of guinea pig complement.

by adding the hemolysin and cells at once without primary incubation. the unit is always smaller than when a primary incubation is given.

2. Primary incubation in a water-bath or air thermostat at 37° C. for one-half hour results in a slight destruction of complement and the unit becomes progressively larger as incubation is continued for one, two and three hours. For example, the unit of a complement without primary incubation was 0.22 c.c. of 1:20 dilution; with one-half hour incubation on a water-bath before the addition of hemolysin and cells, the unit was 0.25 c.c. and after one, two, and three hours of primary incubation the units were 0.32, 0.33 and 0.34 c.c., respectively.

3. Complement deteriorates in an open water-bath at 37° to 38° C. to a somewhat greater degree than in an air thermostat at the same temperature for the same period of time.

4. The hemolytic activity of complement is slightly reduced by a primary incubation of four to eighteen hours at 8° C.; for example, the unit of one serum without primary incubation was 0.2 c.c. of 1:20 dilution and 0.25 c.c. after a primary incubation of eighteen hours at 8° C.

5. When complement is titrated in the presence of an antigen, hemolytic activity is reduced by a primary incubation at 38° C. and at

lower temperatures varying from 2° to 8° C. *but especially at 8° C.* Complement alone suffers but slight deterioration at 8° C. for four to eighteen hours but in the presence of antigen hemolytic activity

TABLE I

THE INFLUENCE OF TEMPERATURE AND DURATION OF PRIMARY INCUBATION UPON
PLAIN COMPLEMENT TITRATIONS

PRIMARY INCUBATION	UNIT COMPLEMENT* 1:20	
	No. 1	No. 2
None	0.8	0.7
38°C. water-bath ½ hr.	0.9	0.7
38°C. water-bath 1 hr.	0.9	0.7
38°C. water-bath 2 hr.	1.0	0.8
37°C. incubator 1 hr.	1.0	0.7
8°C. refrigerator 4 hr.	0.9	0.9
8°C. refrigerator 20 hr.	1.1	1.0
8°C. refrigerator 4 hr. + 38°C. ½ hr.	1.0	0.9
8°C. refrigerator 4 hr. + 38°C. 1 hr.	1.0	0.9
8°C. refrigerator 20 hr. + 38°C. ½ hr.	1.0	1.0
8°C. refrigerator 20 hr. + 38°C. 1 hr.	1.1	1.0

*Titrated plain with 2 units antisheep hemolysin and 1 c.c. of 2.5 per cent suspension of corpuscles; no organ extract.

TABLE II

THE INFLUENCE OF TEMPERATURE AND DURATION OF PRIMACY INCUBATION UPON
THE RESULTS OF COMPLEMENT TITRATIONS IN THE PRESENCE OF
CHOLESTEROLIZED EXTRACTS (ANTIGENS)*

KIND OF INCUBATION	UNITS OF COMPLEMENT 1:20			
	Serum 1	Serum 2	Serum 3	Serum 4
None	0.2	0.2	0.25	0.25
38°C. water-bath 1 hour	0.25	0.25	0.25	0.25
38°C. water-bath 2 hours	0.4	0.4	0.25	0.25
38°C. water-bath 3 hours	0.4	0.4	0.25	0.25
38°C. water-bath 4 hours	0.6	0.4	0.25	0.25
6°C. Refrigerator 1 hour	0.2	0.2	0.25	0.25
6°C. Refrigerator 2 hours	0.2	0.2	0.25	0.25
6°C. Refrigerator 4 hours	0.2	0.2	0.25	0.25
6°C. Refrigerator 4 hrs. + 38°C. 1 hr.	0.25	0.25	0.25	0.3
6°C. Refrigerator 21 hrs.	0.3	0.3	0.25	0.25
6°C. Refrigerator 21 hrs. + 38°C. 1 hr.	0.4	0.4	0.25	0.3
2°C. Refrigerator 4 hours	0.2	0.2	0.25	0.25
2°C. Refrigerator 4 hours + 38°C. 1 hr.	0.25	0.25	0.25	0.25

*Antisheep system; 1 unit hemolysin and 0.2 c.c. of 2.5 per cent suspension of cells added after each primary incubation.

is reduced to a greater extent, due to the anticomplementary activity of the extract under these conditions; for example the unit of a complement titrated in the presence of an antigen without primary incubation was 0.25 c.c. of 1:20 dilution; after a primary incuba-

tion at 8° C. for four hours the unit was 0.37 c.c. and after eighteen hours the unit was 0.43 c.c.

6. When complement with or without antigen is incubated at 8° C. for three to eighteen hours followed by one hour in a water-bath at 38° C. before the addition of hemolysin and corpuscles, the hemolytic activity is still further reduced. For example, the unit of a complement titrated in the presence of antigen without a primary incubation was 0.27 c.c. of a 1:20 dilution; after a primary incubation at 8° C. for four hours the unit was 0.37 c.c. and with an additional hour at 38° C. the unit was 0.41 c.c.; after eighteen hours at 8° C. the unit was 0.42 c.c. and after an additional hour at 38° C. the unit was 0.45 c.c.

CONCLUSIONS

1. The hemolytic activity of guinea pig complement is reduced by primary incubation at 38° C. and especially in a water-bath for one hour; this partly explains the stronger Wassermann reactions observed after a primary incubation of one hour in a water-bath as compared with one hour in an incubator.

2. The hemolytic activity of complement is slightly reduced by primary incubation at 2° to 8° C. for four to eighteen hours, *but markedly reduced under these conditions when titrated in the presence of antigen.*

3. When complement-fixation tests in syphilis are conducted with a primary incubation of four to eighteen hours at 2° to 10° C. with or without an additional incubation of one half to one hour at 38° C., stronger reactions may be expected with some sera, due in part to the greater destruction of complement and consequent closer adjustment of the hemolytic system under these conditions than occurs during the usual primary incubation of one hour at 38° C.

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CHOLESTERINEMIA AND THE WASSERMANN REACTION*

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THERE seems to be no doubt that the so-called Wassermann reaction is continuing to fall into disrepute. When it was first given to the professional world it was hailed as one of the greatest advances made to clinical medicine, and justly so. But it soon fell into the hands of ultrascientists, into the hands of those who insisted on "refinements" of technic, on endeavors to make the test more delicate, on attempts to make it an artificial test: and the result was the revelation that the famous test was, perhaps, after all, not a specific reaction, and therefore at once ceased to be the exceedingly valuable diagnostic and therapeutic test it is entitled to be.

It has been well said that "the generation that holds the responsibility for the future is being inculcated with an almost reverential respect for artificial methods that neither clinician nor pathologist can explain or control."¹ That tendency is an unfortunate one, for it most certainly tends to regard a laboratory test as more important than the patient. We are slowly breaking away from the fallacy of treating the disease rather than the patient. Let us, also, not forget the patient in the making of a diagnosis, and if laboratory tests are to be used to assist us, let us at least remember the patient and his clinical and metabolic state, in our endeavor to interpret what the test tube has shown us.

That is the position in which we find the Wassermann reaction today. It is being done, it is being "refined" and improved and made more "delicate" and positive, and it is being interpreted, with an utter disregard of the patient. We are wont to look upon the patient as a constant factor in the performance of laboratory tests, whereas the patient is without doubt the most inconstant factor. It is needless to recount the variations in the clinical and metabolic states of different individuals, and the continuous variations in the clinical and metabolic states in the same individual. But we give no heed to them, and prefer to juggle and play with the factors that go to make up a so-called Wassermann reaction; our interpretations and con-

clusions are based on the results of our juggling and play. That is the trouble with the Wassermann reaction, and it behooves the serologist and pathologist to come out of the dazzling light of the laboratory and have an occasional look at the patient.

We were wont to look upon the Wassermann reaction as a specific reaction in the diagnosis of syphilis. A reaction of this sort should be a specific reaction, but it is very doubtful whether any complement fixation, depending upon hemolytic inhibition for its interpretation, can be a specific reaction. If the lipid elements of the blood play so important a role in fixation tests of this sort, it is very questionable whether a "notable advance" was made in the preparation of an antigen following the suggestion of Hans Sachs to combine cholesterol with alcoholic extracts of animal organs. Sachs² found that the addition of cholesterol to extracts of organs (however unsatisfactory they were alone) endowed them with properties equal to those possessed by the best syphilitic extracts. This attempt to improve the antigen and to "fortify" it was the beginning of our trouble: and our trouble has continued and grown greater because of continued attempts at "improvements."

If cholesterol artificially added to an antigen enhances the reaction, it is logical to conclude that, perhaps, the reaction itself is dependent upon cholesterol. For each animal organ is known to contain cholesterol and an alcoholic extract of any organ will contain various amounts of cholesterol. Several years ago I determined the cholesterol content of alcoholic extracts of guinea pig and human heart; the figures follow:

Guinea Pig Heart in Alcohol.

3 months old.....	1c.c. extract contained 0.00023 gms. Cholesterol
	1c.c. extract contained 0.00024 gms. Cholesterol
6 months old.....	1c.c. extract contained 0.00030 gms. Cholesterol
	1c.c. extract contained 0.00036 gms. Cholesterol

Human Heart in Alcohol.

12 months old.....	1c.c. extract contained 0.00032 gms. Cholesterol
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These amounts are approximately the same found in human spinal fluid and in transudates, and are about one-fifth to one-sixth of the amount found in normal human serum. While figures for liver, spleen and pancreas are not immediately available, we have every reason for believing that the amounts of cholesterol to be found in these organs are greater than those found in the heart.

It has been due to the use of various antigens that we have lost faith in the Wassermann reaction, and especially in its specificity. The finding of a so-called positive Wassermann in conditions other than syphilis is certainly no reason to shake our faith in the reaction. Such findings, with the possible exception of yaws and leprosy, are without doubt due to technical errors, or to the fact that the cholesterinemia in those conditions is influencing the reaction and therefore upsetting our interpretation.

Bittorf³ calls attention to the appearance of positive Wassermann findings in nonsyphilitics after injury or destruction of organs particularly rich in lipoids, as with cancer of the liver and tumors of the brain and spinal cord. But there is no reason why the Wassermann reaction should be interpreted as positive in these conditions simply because inhibition of hemolysis was found in the test. We are now well aware of the fact that a hypercholesterinemia is to be found in such conditions as Bittorf mentions. He also found positive reactions in typhus fever, a condition in which the liver and brain and spinal cord are especially involved. Such findings merely indicate the necessity for a correct interpretation of the Wassermann reaction.

The experience of Daland⁴ is one that I have frequently had. He speaks, and rightly names it, a "pseudo-positive" Wassermann reaction in a case of uremia on the basis of a chronic interstitial nephritis. Four Wassermann tests taken at intervals during the two weeks following the patient's admission to the hospital showed one 3-plus, two 1-plus, and one plus-minus reaction. The cholesterinemia in chronic nephritis, especially in uremic states, has been carefully studied⁵ and it is generally agreed that the measure of cholesterinemia steadily falls in uremic states terminating fatally. But the interpretation of a Wassermann reaction in such a condition must take the fall in the cholesterinemia into consideration, for that fall is equivalent to the "weakening" of the antigen. The experience of Verdozzi and Urbani,¹⁴ who found in all but 5 of 26 cases of chronic diseases of the liver (in cases in which there was nothing to suggest syphilis) positive Wassermann reactions, is not startling, if one considers that hypercholesterinemias are very frequently found in such conditions.

It is now a well-known fact, also, that the reaction is enhanced and intensified by the use of larger amounts of patient's serum in the test.⁶ The reaction negative with 0.1 c.c. of serum is frequently found

positive with larger amounts, but in using the larger amounts it must not be forgotten that more cholesterol is being used, and we must interpret the reaction with that fact in mind. The serologists using smaller doses of serum, (0.1 c.c.) use relatively very large doses of antigen extract. The use of a large dose of antigen extract is equivalent to the use of a large dose of serum as far as the amount of cholesterol in the make-up of the component parts of the test is concerned.^{7, 8, 13}

The excellent work of Walker⁹ shows clearly the influence of the amount of cholesterol in the make-up of the reaction. He found that the amount of serum necessary to give fixation, ("Fixing Unit") varied greatly in different persons and in the same person in different stages of the disease. "On the other hand, after the required amount of serum necessary to give fixation was determined, the amount of antigen remained constant for different persons in the same stage of the disease. Having found by titration the least amount of serum required to give fixation with the standard amount of antigen, and then determining the least amount of antigen required to give fixation with the least amount of serum, a definite increase in the amount of serum caused a proportionate definite decrease in the amount of antigen necessary to give fixation. Cholesterin is the specific agent, which in the presence of complement, combines with syphilitic serums." Walker in his work used a cholesterin reinforced antigen and his "fixing unit" determinations are certainly dependent upon the amount of cholesterol in the make-up of the reaction. It is of interest to note that with the use of cholesterinized antigens the amount of cholesterol in the make-up of the reaction (and by "make-up" is meant, (a) patient's serum, (b) antigen, (c) complement, (d) cell emulsion, and (e) amboceptor) is considerable.

Taking the cholesterol content of normal human serum to be approximately 0.002 grams per 1 c.c. (it is a little less than that amount), the amount in 0.1 c.c. of serum would equal 0.0002 gms. In the preparation of his fortified antigen Walker proceeds as follows: 0.1 gm. of cholesterol is added to 25 c.c. of an alcoholic extract of heart; 1 c.c. of this 0.4 per cent cholesterol extract is added to 9 c.c. of 0.85 per cent saline, and 0.5 c.c. of this 1/10 emulsion is used as antigen in each tube. In each tube, therefore, we would have,

0.1 c.c. of serum equals	0.0002 gms. of cholesterol
0.5 c.c. of antigen equals	0.0002 gms. of cholesterol
	<hr/> 0.0004 gms. of cholesterol

The plain alcoholic extract of heart already contains at least 0.0002 gms. per 1 c.c. It is at once seen, therefore, that each tube, when a fortified antigen is used, contains at least 0.0005 gms. of cholesterol, an amount that is normally found in human spinal fluid and transudates, and approximately 25 to 33 per cent of the amount found in normal blood serum.

We are well aware of the variations of the cholesterol content of the blood in different pathologic conditions and the variations at different times in the same pathologic condition. There are, also definite variations under normal conditions—as in pregnancy—and striking variations under different physical conditions—as in fever. Sufficient work has now been done to enable the clinician to know when to expect a hyper- or a hypo-cholesterinemia. In my own experience I have seen variations ranging from 0.0004 to 0.01028 grams per 1 c.c. of serum. If such variations in serum cholesterol are disregarded when performing a Wassermann reaction, it is no wonder that we have “technical difficulties” and cannot agree on a proper interpretation of the test. Even granted that serologists will get together and standardize the technic of the test, it will avail us nothing so long as we continue to disregard the fluctuations in the cholesterol content of the serum. To properly interpret the Wassermann reaction, it is my belief that we must be fully aware of the biologic state of the individual whose blood is to be examined, and of those physical and chemical (metabolic) states which we know influence a reaction of this sort.

At a meeting of the Society for Serology and Hematology of New York, April 2, 1915, this subject¹⁰ was presented at a time when serologists were making use of fortified antigens for only a comparatively short time. A cholesterinized antigen has not become less popular since that time—on the contrary, at the present time it is being used quite generally. And yet, the attitude toward the Wassermann reaction continues critical and the lack of faith in this exceedingly important diagnostic procedure is not diminishing—on the contrary it is increasing. Serologists are at loggerheads; many workers have a dogmatic assurance that the particular method that they employ gives the best results. Serologists cry out for “standardization of technic:” true, “standardization” will eliminate the inconsistencies in reports from different laboratories on the same blood specimen, but “stand-

ardization of technic" alone will not help us in our endeavor to correctly interpret, and thereby actually profit by the result of the reaction. In my original paper on the subject,¹⁰ I made bold to say that no earnest serologic work today can be properly explained or correctly interpreted without due regard to the cholesterin and lipid content of the blood. Despite all that has been said and written on the subject in the ensuing years, in fact, because of all that has been said and written on the subject since 1915, it seems to me that my remarks deserve further emphasis. The serologist has since then not helped the clinician in the interpretation of the Wassermann reaction, and I still maintain that the serologist is groping in the dark because he fails to consider that very substance of the blood which he uses to "fortify" the antigen, and to increase the delicacy of the test.

Reference to the literature of recent years will show that both clinician and pathologist are still unable to agree on the value of the Wassermann reaction. The conclusions reached by some investigators are distinctly discouraging.

"Depending on the antigen employed the Wassermann reaction in the living patient gives a negative result in from 31 to 56 per cent of the cases in which the characteristic anatomic signs of syphilis are demonstrable at necropsy." "The Wassermann reaction in the living patient is positive in at least 30 per cent of cases in which it is not possible to demonstrate any of the anatomic lesions of syphilis at necropsy." These conclusions of Symmers, Darlington and Bittman¹ are, I believe not to be taken seriously, especially in so far as the interpretation of the Wassermann reactions are concerned. Personally, I prefer to give more credit to the test, and agree with the "Reply" of Larkin, Levy and Fordyce¹¹ that "the term 'Wassermann reaction' includes several methods of serologic procedure. An accurate interpretation of each method is essential in arriving at a proper diagnosis." I prefer to agree with the latter investigators that "the reaction is positive in practically 100 per cent of cases of florid syphilis and in about 94 per cent of cases of active tertiary syphilis." Ottenberg⁷ also concludes that the Wassermann reaction is "reliable and diagnostic of syphilis."

As has been said previously, the use of a cholesterinized antigen has come into pretty general use, and most serologists are agreed that such an antigen has the following so-called "advantages:"

1. Enhances the reaction.
2. Hastens the reaction.
3. Increases the delicacy of the reaction.
4. "Discovers" more positive reactions.
5. The reaction is kept positive longer.
6. More likely to "detect" latent syphilis.

But the serologists have, in their enthusiasm, I believe, also brought to light the great disadvantages of the use of cholesterinized antigens. As Ottenberg⁷ correctly says, "It is true of any antigen, that the greater the amount one can use of it, the more delicate the test: but that the nearer one approaches the amount that begins of itself to become anticomplementary, the greater the danger of nonspecific fixation." That remark, to my mind sums up the whole and great disadvantage, and at the same time the danger of using cholesterinized antigens. For as long as we disregard the cholesterol content of the serum to be tested, we cannot possibly know how "near one approaches the amount that begins of itself to become anticomplementary." Surely the cholesterinemia of 7.97 gms. of a chronic nephritic approaches the danger mark of nonspecific fixation, closer than does the cholesterinemia of 2.00; and surely in a known syphilitic with an accepted positive Wassermann, the degree of hemolytic inhibition will be different, at different times depending on the cholesterinemia each time the blood is tested.

With spinal fluids the use of strong antigens, or the use of far greater amounts of antigen than are used with blood serum, we are told by the serologists have been found "safe" and to detect reactions which would otherwise be lost. But in saying this the serologists fail to appreciate the fact that the cholesterol content of spinal fluids is also subject to considerable variations, depending upon the nature of the process involving the meninges. Adjusting the dose of the antigen to the complement or adjusting the dose of the complement to the antigen, in attempting to solve the important subject of dosage of antigen, is futile so long as the cholesterol content of the patient's serum or spinal fluid is unknown or disregarded. This fact is emphasized by the findings of Kolmer, Heist, Trist and Pearce¹² who observed that the extraction of suitable serums with ether and chloroform, usually diminished the antilytic and complement fixing powers of a serum, whereas the administration of lipoids increased the antilytic and complement fixing powers.

To me there seems to be no doubt that many of the unfavorable reports on cholesterinized antigens in the literature are due, not to an antigen dose which is relatively too great, but to the fact that the cholesterol content of the patient's serum is not known, and even if it is approximately known (from experience and facts which are available) it is not given the attention it deserves in any attempt to interpret the reaction. Careful serologists admit that cholesterinized antigens, while they give a far greater number of weak positive reactions in known and treated syphilis, also give a considerable number of false positive reactions in cases surely not syphilitic.

We are told that weak inhibitions with cholesterinized antigens should not be given great weight except in known cases of syphilis: we are further told that positive results with it alone in pregnancy should be disregarded. It is a well-known fact that there is a steady rise in the cholesterol content of the blood in cases of pregnancy, a rise that is transitory and continues only until delivery. Walker's⁹ statement that a "positive Wassermann, properly done, with or without a history of infection, does mean syphilis" cannot be subscribed to, but I heartily agree with him when he says, "that a definite amount of cholesterin is necessary for the fixation of a definite amount of serum, and varying the amount of serum likewise varied inversely the amount of cholesterin." We cannot possibly know what this "definite amount" of cholesterin is so long as we regard the variations of the cholesterol content of the blood serum.

In the matter of treatment the Wassermann reaction is of great value. In latent or occult syphilis, and as a guide to treatment, the reaction is of particular and special value. It is generally agreed that the use of cholesterinized antigens in a known case of syphilis is of great value because in many cases it continues to give weak positive reactions long after the reaction to simple antigens has disappeared. Its application as a control on treatment at once becomes apparent. But a persistent positive reaction with cholesterinized antigens, in a case under proper treatment does not always mean that the case is actually actively syphilitic. Admitting that serum cholesterol will influence the reaction, and in cases of hypercholesterinemia it will bring the reaction to and even beyond the danger mark of nonspecific fixation, it is very questionable whether a positive Wassermann alone prohibits matrimony, as Heimann¹⁵ maintains. Under the circumstances, the contentions of Keyes¹⁶ seem

more logical. He insists that a positive Wassermann, *per se*, does not prohibit matrimony. He further correctly concludes that "a fixed positive Wassermann reaction in later years of the disease does not inevitably point to the prospect of grave lesions." Keyes, too, (as have I) has seen cases in whom the Wassermann reaction remained fixed for many years despite the most violent treatment, the patients "all the while persisting in smiling health despite the disease and despite the treatment." It is my belief that such reactions remain fixed because of the presence of a hypercholesterinemia.

In my original paper on this subject¹⁰ several questions dealing with hypothetical cases were asked; they are repeated.

No. 1. Has the Wassermann reaction in a pregnant woman ever changed from 2-plus to 4-plus during the course of the pregnancy, despite treatment? While I cannot find the report of such an occurrence in the literature, it is the serologists themselves who ask us to be very careful in our interpretation of a Wassermann reaction in pregnancy. Falls and Moore¹⁷, remark that "it will be seen, therefore, that any condition such as pregnancy in which the lipoidal contents of the blood are increased, an interference might theoretically be expected in the reaction that depends for its specificity on the presence of lipoidal bodies." With the use of cholesterinized antigens, and in the light of our present knowledge of the so-called "value" of such "fortified" antigens, something more than a "theoretical interference" is to be expected. It seems to me that we are dealing with an actual interference.

Cornell and Stillans¹⁸ in their paper speak of a case of a pregnant woman with a positive reaction before parturition, and a negative reaction a few days after delivery. In this case treatment before delivery had failed to influence the positive reaction. The recognized and accepted fact that the hypercholesterinemia of pregnancy disappears after delivery is, I believe, the explanation of the change in the Wassermann reaction.

No. 2. Has the 4-plus reaction of a chronic nephritic ever changed to 2-plus when that patient became uremic and died, even without antisyphilitic treatment? This observation has been frequently made and previous mention of it has been made.

No. 3. Is the Wassermann reaction influenced at all by fever? We have since learned that we prefer to do a Wassermann reaction in the absence of fever. In the fever period of our pneumonias we

frequently obtain puzzling results. And it is a recognized and accepted fact that the cholesterinemia is diminished as the result of fever.

No. 4. Why does an icteric serum frequently inhibit hemolysis? "When the jaundice disappeared the reaction became negative." Walker⁹ is not the only one who has made that observation. And it is recognized and accepted that in conditions of jaundice a hypercholesterinemia is also found.

No. 5. Has the intensity of the reaction ever increased in a convalescent case of typhoid fever? Reference to recent literature does not answer that question, but I believe it will be found to be true: the measure of cholesterinemia is known to be increased during convalescence from typhoid fever.

No. 6. Do not old syphilitics, old with endarteritis and arteriosclerosis, resist treatment; that is, do they not persist with their strong positive reactions? Decidedly yes, as has been frequently observed.

And finally: Has a positive Wassermann reaction ever become spontaneously negative? That, too, can be answered affirmatively, and Keyes¹⁶ remarks, "In two instances I have seen a positive Wassermann reaction become negative spontaneously, although vigorous treatment in the preceding years had failed to make it so." I believe the measure of cholesterinemia in these two instances would prove explanatory.

In any intelligent interpretation of the Wassermann reaction the measure of cholesterol in the fluid that is to be examined, be that fluid blood serum, spinal fluid, transudate or exudate, must be taken into consideration. The smaller the amount of contained cholesterol in any given fluid, the stronger will the Wassermann reaction be with that fluid. It is never to be forgotten that pathological hypercholesterinemias tend to make the serum approach that danger mark where the serum itself, and of itself, will become anticomplementary and inhibit hemolysis. This, of course, applies especially in known cases of syphilis, where a positive Wassermann reaction might be the cause of great injustice to the patient, and result in needless and useless treatment. A 4-plus reaction with a hypercholesterinemia is a weaker reaction than a 4-plus reaction with a normal cholesterinemia; a 4-plus reaction with a marked hypercholesterinemia is no stronger than a 2-plus reaction with a moderate hypercholesterinemia; a 4-plus reaction in a pregnant woman is a weaker reaction than a 4-plus re-

action in a nongravid woman; a 4-plus reaction in a chronic nephritic is a weaker reaction than the 4-plus reaction of another chronic nephritic in a uremic state; a 4-plus reaction in a diabetic with acidosis is a weaker reaction than the 4-plus reaction in a diabetic without acidosis; a 4-plus reaction in the presence of jaundice is a weaker reaction than the 4-plus reaction in the absence of jaundice, etc. It is not necessary (although it would be of more actual help) to know definitely the measure of cholesterinemia in any given case, but the state of the individual, in so far as that state influences the cholesterinemia, should certainly be included in any estimate of the value and significance of the Wassermann reaction.

From all that has been said and written, are we not justified then in concluding that serum cholesterol and the measure of cholesterinemia are very important factors, if not essential factors, in the proper interpretation of the Wassermann reaction, no matter what antigen is used, and no matter whether the technic for the test is standardized or not. True, a standard test cannot be too strongly advocated; but, if we are to avoid discrepancies, if we are to give the reaction the value it deserves, if we are to restore faith in the reaction, and if we are to derive most (and truthful) benefit from the reaction, it seems to me that we must never forget the patient when the test is done and interpreted: we must know and appreciate those conditions which influence the measure of cholesterinemia, both under normal and pathologic conditions, and take them into consideration. Let us not be "dazzled by the splendors of twentieth century science;" let us, rather, remember that the Wassermann reaction is, perhaps, not so mysterious as we think it is.

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THE PREPARATION OF AMBOCEPTOR WITH HUMAN ERYTHROCYTES*

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FOR nine years at the Mayo Clinic we have employed the human erythrocyte hemolytic system as the index in the Wassermann reaction. We have also made use of the acetone insoluble fraction antigen for routine work. In other words, the serologic method employed in about 100,000 examinations has been practically the Noguchi modification of the Wassermann test. During this period various other modifications have been tried, the human-cell system, the sheep-cell system, and the chicken-cell system, and various types of antigens, such as alcoholic-heart-muscle extracts reinforced with cholesterol, and alcoholic extracts of syphilitic fetal livers. We are still using with satisfaction the system which is nearly the same as that outlined by Noguchi several years ago. The only change in technic that we have found of advantage is in the addition of amboceptor in mass to a given quantity of washed cells, a procedure employed by many serologists who use a sheep-cell system. The union of the amboceptor and cells takes place overnight in the ice-box, or if this is not possible in about thirty minutes in the incubator the day of the test.

There are many advantages in the use of human cells in serologic work in an institution such as ours. In the first place, we had some difficulty in the satisfactory management of a constant source of sheep-cells, either when we attempted to get them from the local butchers, or when we kept animals of our own.

Contrary to the situation in many laboratories, however, we have no trouble in getting large quantities of human blood. Many nearly normal persons are sent daily for venipuncture for various tests. In fact, the complement deviation tests for any day are done on the blood of patients who have been bled that morning by the tech-

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nicians who assist in carrying out the tests. Our system has been developed so that it is possible for six persons to bleed 100 or more patients in about two hours and to carry out the serologic technic on the freshly centrifuged serum. The report is ready for the clinician early in the afternoon of the same day that the patient is bled. There is thus no variation in the different serums, neither are we troubled with anticomplementary substances developing from either age or bacterial contamination. We are also able to obtain from these patients pools of blood that will give cell suspensions of any quantity that might be required either for injecting animals or for the daily test.

Theoretically there are advantages also in the use of the human-cell over sheep-cell or chicken-cell systems. We are greatly indebted to Dr. Kolmer and his colleagues for their many excellent studies on the standardization of the Wassermann reaction. Kolmer, Trist and Flick (in Study VII) have made an investigation of the natural thermolabile and thermostabile hemolysins and hemagglutinins in human serum with relation to the Wassermann reaction. While it may appear that most of this study does not pertain to my subject, I shall call attention to the twelfth conclusion of the paper.

"In reference to the Wassermann and other complement-fixation tests the presence of natural hemolysins and hemagglutinins in human sera are important in relation to the hemolytic system; theoretically at least the presence of a natural hemolysin for the corpuscles of the indicator antigen tends to disturb quantitative conditions in the hemolytic system and to reduce the delicacy of the complement-fixation test, while an agglutinin may interfere with hemolysis, particularly with a low titer rabbit-immune hemolysin and thereby interfere with the sharpness of the reaction. *Judged solely on this basis human corpuscles are best adapted for complement-fixation tests employing active or unheated sera; with inactivated or heated sera, human or chicken corpuscles are best suited.** Other factors, however, are to be considered before a decision can be made on the best hemolytic system for a standardized technic, namely, the actual rather than theoretic influence of natural hemolysins and hemagglutinins and practical means for overcoming their influence, the ease, or difficulty by which blood is obtainable, and more particularly by the ease or difficulty by which immune hemolysins are prepared by injecting the corpuscles of persons and various of the lower animals *into rabbits.*"

*Italics mine.

The chief disadvantages in the antihuman system, as I have often heard it expressed by various serologists in different parts of the country, is this difficulty in making a satisfactory amboceptor. Rabbits do not respond so rapidly to injections of human cells as they do to sheep cells in the preparation of a high titer hemolysin, but perhaps the chief objection to the use of a rabbit serum immunized to human erythrocytes is the fact that often although a fair amount of hemolysin may have developed there is also a very large amount of agglutinin for human cells. This has not been considered a great objection by some serologists. It is true that when amboceptor is added separately at the end of the first period of incubation, frequent shaking of the tubes will break up the clumps of agglutinated erythrocytes so that complete hemolysis may occur, and satisfactory observations be made. However, it is almost impossible to use rabbit serum to "sensitize" red cells if it contains a large amount of hemagglutinin.

A recent paper by Sands and West has dealt extensively with possible procedures for the removal of hemagglutinin in antihuman serum. They point out five methods by which the agglutinin may be removed from serum in such a manner that it may be rendered fit for use, the hemolytic properties still remaining. They state first that rapid filtration, in itself, will remove some agglutinin. They also find that drying on filter paper removes the agglutinin so that when the serum is redissolved only the hemolysin is free. I may say that while this may be true in their experimental work, I found, several years ago, that it is not a practical method for removing agglutinin. I have prepared many samples of amboceptor, drying the serum on filter paper, and have found that although small pieces of amboceptor-saturated filter paper might be added to the individual test tube, according to the Noguchi method, with no trouble from agglutinins, it was almost impossible to add large pieces of paper so prepared to a considerable mass of cells in the attempt to sensitize them. Sands and West also report the removal of agglutinins by barium sulphate. Large quantities of washed red blood cells will also absorb the agglutinin. Hypotonic salt solution will remove the agglutinin and leave the serum active in hemolysin. All their experiments are of interest from the theoretic standpoint. In practice, however, I believe that we have a simpler solution of the problem of the preparation of amboceptor with human erythrocytes.

About three years ago it occurred to us that the slight amount of natural hemolysin found in dog serum for human red blood cells might be increased if this animal were used for the preparation of amboceptor. Much to our gratification the immunization of a dog with washed human red blood cells produced a very good grade of amboceptor. Since that time these animals have been employed almost exclusively in the preparation of hemolysin. The technic is much the same as when rabbits are used, all of the injections being given intraperitoneally. A dog about the size of a fox terrier is preferred as these animals produce an amboceptor in a comparatively short time and their size makes them more easily handled for repeated injections. Moreover, the size of the dose may be kept within reasonable limits more readily than when large dogs of the collie or Airedale types are employed. The amount of blood that may be obtained by bleeding from the heart of a terrier is usually from 250 to 400 c.c., and from this quantity 100 to 200 c.c. of very good serum may be obtained. The procedure is briefly as follows:

A considerable pool of human blood is obtained from several different patients; this is placed in a 250 c.c. flask containing 50 c.c. of a 2 per cent sterilized solution of sodium citrate. These cells are washed five or six times with normal salt solution with repeated centrifugalizations and a 50 per cent suspension of cells made in normal salt solution. For a small dog the initial injection is about from 30 c.c. to 35 c.c. intraperitoneally, the second week 40 c.c., the third week 50 c.c. At the end of seven days 2 or 3 c.c. of blood are aspirated from the animal's heart. The serum of the blood withdrawn is then titrated for amboceptor, using a double unit of complement, usually 0.1 c.c. of 40 per cent guinea pig serum in normal salt solution. Occasionally a very good hemolysin develops in so short a time. It is usually necessary, however, to give, at this time, another injection of from 50 c.c. to 60 c.c. and we have also given, in some instances, a fifth injection of from 50 c.c. to 60 c.c. of a 50 per cent suspension of cells, all injections being given at intervals of from seven to ten days. When an amboceptor of fairly good titer has been obtained, the animal is etherized and bled from the heart to exsanguination. We have found that the simplest manner of bleeding all large animals is to use 20 c.c., 30 c.c., or 50 c.c. all-glass syringes. One hundred cubic centimeter syringes have been tried but found too cumbersome. A quick direct stab into the heart is made with a long, large bore needle. The

blood comes very rapidly as long as the animal is alive and the heart pulsating. By the aid of a skilled assistant and by using several sterile syringes, the blood may be aspirated more rapidly by gentle suction than if allowed to flow directly into the collecting vessel. If the blood ceases to flow readily into the syringe, the needle is withdrawn and a new needle is used with other sterile syringes. Needles and syringes are sterilized by boiling in water at the time the bleeding is done. The blood is placed directly into sterile 50 c.c. centrifuge tubes and is centrifugalized at once, before clotting takes place if possible. This makes a clear clot in the upper portion of the tube which is separated and the blood further centrifugalized for several minutes. The sterile cotton plugs are held in place by means of rubber bands. After the clot is separated and the serum begins to be expressed the tubes are placed in the ice box. The next day the serum is removed, inactivated for thirty or forty minutes at 56° C., and titrated for amboceptor content. We do not, as a rule, obtain amboceptor of as high titer, that is, 1:1500 or 1:2000, as may be obtained at times with some strains from rabbits. In fact, the dog does not generally produce a very high titer amboceptor; 1:500 is about the average. The outstanding features, however, are that very little, if any, agglutinin is produced, that the serum may be added to the cells in a mass, that a great deal of time may be saved by working with these sensitized cells, and that the hemolysis which occurs is clean-cut with no chance of doubt because of clumps of agglutinated corpuscles at the bottom of the tubes.

These few suggestions are offered with no desire to add another modification to the too long list of new serologic methods for the diagnosis of syphilis. I believe, however, that our experience warrants the statement that the dog may be used to better advantage than the rabbit in the preparation of amboceptor with human erythrocytes.

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SPONTANEOUS RUPTURE OF THE HEART AND AORTA*

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A CAREFUL review of the literature and autopsy statistics from some of our large hospitals reveals the fact that spontaneous rupture of the heart and of the aorta are rare lesions. These pathologic entities are of particular interest to the pathologist, for their diagnosis is generally not made during life and they are usually encountered only at the autopsy table. Very frequently these lesions are of considerable medico-legal interest.

The following two cases came to autopsy and illustrate rather well the interesting conditions.

CASE 1.—The subject was a young negress, about twenty-two years of age, found dead in bed in a lodging house. No other history was obtainable. Two interesting lesions were found at autopsy, namely, a gumma of the spleen and a ruptured gumma about $2\frac{1}{2}$ cm. in diameter situated on the anterior surface of the left ventricle of the heart near the apex. The tear in the gumma was ragged and extended obliquely through the muscle. The pericardium was distended with blood (Fig. 1).

CASE 2.—The subject was a white male, about forty-five years of age, found dead in the lavatory of a train while en route to New York City. No further history was obtainable. Externally, there was a small scar on the corona of the penis. No other injuries or anomalies were present on external examination. The pericardial cavity was distended with partially clotted blood. About $1\frac{1}{2}$ cm. from the ostium of the aorta there was a clean, smooth-margined tear which involved the vessel wall through its entire thickness and circumference, with the exception of about $1\frac{1}{2}$ to 2 cm. The walls of the organ were thin, but smooth and fairly elastic; it was diffusely dilated, but showed no pathologic changes visible to the naked eye. The liver showed a diffuse cirrhotic process (Fig. 2).

The lesion pictured by Case 1 is readily appreciated and is reported only because this type (large gumma in the heart muscle) is extremely rare and is not noted in any of the ordinary text-books on pathology as a cause of cardiac rupture. The lesions produced by syphilis

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Fig. 1.



Fig. 2.

in the heart are generally fibrous changes with round-cell infiltration and atherosclerosis in the blood vessels.

Reports in the Continental journals and publications on ruptured hearts are not infrequent, some dating back to 1733. Spontaneous rupture of the heart was known to William Harvey and several cases were described by Morgagni in his writings. Of the more modern literature dealing especially with the etiology and symptomatology of this condition, the publications of Barth, Robin and Meyer are of interest. The last-named author reports eight cases which had been under medical observation for some time prior to death. In many of these cases a history of myocardial affection followed by sudden death disclosed, at autopsy, a ruptured, diseased heart muscle. It is conceivable that if more cases of chronic heart disease terminating in sudden death were autopsied, we would find ruptured heart muscles more often.

Rupture of the heart is generally found in old people. The lesion predominates in males, and the greatest age incidence is between 60 and 65 years. Its most frequent site is in the left ventricle, and it is often associated with an infarct and subsequent necrosis and softening (myomalacia) of the muscle. Much less frequently fatty degeneration, atrophy, abscesses, tumors, cysts or aneurysms of the heart have been implicated in the production of this lesion. Cases have been described from time to time in which the normal heart muscle was torn as the result of extreme physical or psychic effort. These cases, however, are open to considerable criticism, for it is quite possible to overlook minute degenerative changes in some part of the organ, particularly in the gross, and even when aided by the microscope—a contention emphasized by Thorel and now accepted as evident.

The lesion of ruptured aorta represented by Case 2 is of considerably greater interest not only because of its rarity, but its etiology also has called forth considerable discussion and experimental endeavor. In this lesion, too, there is a division of opinion as to whether or not a pathologic change in the vessel wall is essential to the production of a tear. The resistance offered by the normal arterial wall to rupture is considerable and is generally underestimated. Grehaut and Quinquad demonstrated in dogs that it took a pressure

of from 7 to 11 atmospheres or a pressure 35 to 56 times greater than normal in order to rupture the carotid vessels of these animals. Such a pressure is never attained during the life of the average man. In sharp contrast to this view, however, it is not infrequent to find an aorta or the much finer or smaller vessels, such as those of the cerebrum, ruptured by the blood pressure, without recognizable lesions either in the gross or microscopically. In such cases, "molecular" disturbances of the elastic and muscle fibers, not visible with the microscope, are supposed to be present. It is quite conceivable, too, that the normal artery in a living subject at times is not capable of responding as promptly or readily to changes in blood pressure, with consequent sudden and extreme increase in the pressure, and, hence, rupture.

Ruptures of apparently normal vessels are found in young people. In such individuals the anatomic defect of status lymphaticus with hypoplasia of the arterial system is often present. Anomalies in the size of the vessels may also be found. Thus, the diameter of the aorta, especially at the commencement of the arch, may be found considerably diminished. Leaving the question of rupture of the normal vessel as the result of great physical exercise or psychic emotion in abeyance, we find that by far the greater number of cases occur in those individuals where the arterial wall has become thinned during the course of an aneurysmal process or other atheromatous or ulcerative lesion of the vessel wall. It is stated that two stages really occur in these individuals, one in which the intima is torn so that the blood gets into the walls of the vessel, running through it and forming a dissecting aneurysm. Sharp pain usually accompanies such a tear. The outer and final tear occurs within a few days to several months, when the process has extended through the wall, causing the patient to collapse and die instantaneously. In the case under discussion, no such lesion could be demonstrated, and the positive etiology remains obscure. Evidences that the individual had had syphilis were present, though it must be recalled that there were no gross lesions in the vessel. Signs of status lymphaticus or other anatomic defects were not present. Microscopic examination of the aorta stained with hematoxylin, eosin, and orcein showed a thin-walled vessel in which the elastic tissue of the media was considerably diminished in amount.

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SYPHILIS OF THE GENITAL ORGANS OF THE MALE AND THE URINARY ORGANS. IV*

SCROTUM, TESTICLE, EPIDIDYMIS, SPERMATIC CORD, SEMINAL VESICLES

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SCROTUM

THE skin of the scrotum may be the seat of nearly all types of the cutaneous manifestations of syphilis, the chancre, macular, papular, pustular, nodular and gummatous lesions are all found in this region.

Although of comparative infrequency, *chancre* of the scrotum undoubtedly was recognized by the early syphilographers, although the first mention of this condition which I can find is by Hunter¹ in his *Treatise on the Venereal Disease* published toward the close of the eighteenth century.

As just stated, the initial lesion of syphilis is rather infrequent in this region. According to Lambkin² of 430 genital chancres in men observed in the Hospital du Midi, 17 occurred on the scrotum and prescrotal angle. These figures are much higher than has been my experience. Of 121 genital chancres in men of which I have record, seen in private, clinic and army practice, only two were on the scrotum. Furthermore of a considerable number of male genital chancres which I have seen, but of which I have no record, I do not recall a single scrotal lesion.

Chancre occurring on the scrotum usually begins as a small, red, circular spot which gradually increases in size. Soon desquamation of the superficial epithelium begins and small cracks occur which form a circular ulcer. The latter is usually shallow and quite indurated.

*This is the fourth of a series of articles dealing with syphilis of the genital organs of the male and the urinary organs. The first, "Syphilis of the Bladder," appeared in the January, 1920, number of this Journal, the second, "Syphilis of the Prostate," in the April, 1920, number; the third, "Syphilis of the Kidney," in the July 3, 1920, number of the *Journal of the American Medical Association*, while the fifth and final article of the series, "Syphilis of the Urethra, Ureter, and Kidney Pelvis," will appear in the January, 1921, number of this Journal.



Fig. 1.—Chancre of the scrotum. (Courtesy of Dr. M. B. Parounagian.)

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Fig. 2.—Lenticular (moist) papular lesion of scrotum. Also vegetating lesions of anus.

The *macular* syphilodermata are rarely observed on the scrotum; in fact, I have never seen such lesions, although it is possible that they do sometimes occur. Neither do I recall having seen the *miliary papular lesions* of this region, but the *lenticular papular*, both the dry and the moist, particularly the latter, are very frequent. Rarely the moist papular lesions take on a decided cauliflower appearance in this region, although such a condition is not so frequent on the scrotum as in some other regions, for example, around the anus.

The very rare *vesicular* and *bullous* syphilodermata have not been described as occurring in this region, and the *pustular* and *nodular* lesions certainly are not frequent on the scrotum. The *gummatous* syphiloderm, on the contrary, is quite often observed, although, as a rule, these lesions occur as an extension from the testicle.

TESTICLE

HISTORICAL

Although one of the most frequent of all the manifestations of the disease, luetic orchitis was apparently not recognized until 1736 when Astruc³ differentiated venereal tumors of the testicle which responded to treatment by mercury and those which did not so respond.

Benjamin Bell⁴ in 1793 clearly pointed out that the testicle could be involved in the syphilitic process when the patient had not suffered from gonorrhea, and based his contentions upon the following: "By the swelling coming on without any external injury; by no gonorrhea having preceded; by the patient being known to be infected with lues venerea at the time; and by the swelling being with ease and certainty removed by mercury while it had daily become worse as long as those remedies were employed which usually prove effectual in swelling of the testes arising from gonorrhea."

In 1830 Sir Astley Cooper⁵ described syphilis of the testicle occurring early in the course of the disease and thought that the "venereal poison" first attacked the tunica albuginea and thence extended into the interior fibrous, and not into the tubular part. Cooper also thought that the disease usually began in both testicles simultaneously.

However, it was not until Ricord⁶ gave the support of his great authority to the question that syphilis of the testicle became gener-

ally recognized. While Ricord admitted that the seat of the process might be in the epididymis, he stated that it was the substance of the testicle which is almost invariably affected. Since the time of Ricord syphilis of the testicle has received a great deal of attention and is now quite thoroughly understood.

FREQUENCY

As stated above, syphilis of the testicle is one of the most frequent manifestations of the disease. The Index Catalogue of the Library of the Surgeon General's Office contains no fewer than 28 references to monographs on the subject and to 123 articles in periodical literature.

However some difference of opinion as to the actual frequency of the condition seems to exist.

Symmers⁷ states that of 171 male subjects of late acquired syphilis in the Bellevue Hospital series of autopsies chronic interstitial orchitis was found 67 times, or in 39 per cent.

On the other hand, Warthin⁸ found varying degrees of atrophy and fibrosis in the testis of all male cases of syphilis which came to the autopsy table at Ann Arbor.

Statistics as to the frequency of the clinical recognition of the condition are not available.

PATHOLOGY

Syphilis of the testicle occurs in two forms, *interstitial*, or *fibrinous*, *orchitis*, and *gummata*. The two forms, however, are quite frequently associated, particularly when gummata exist when there usually is also more or less interstitial sclerosis.

The interstitial type is usually of earlier occurrence than the *gummatous* type, being observed as a rule during the first three or four years, although rare before the second year. Keyes⁹ observed one case before the seventh month, while Power¹⁰ reports a case in a man of eighty, whom he states must have contracted his syphilis at least sixty years before.

The condition may be bilateral, although more frequently it is unilateral and the swelling may be so slight as to pass unnoticed, or the organ may become several times its normal size. Not infrequently fluid develops in the tunica vaginalis, although as a rule this is rather small in amount. Histologically the process consists of an



Fig. 3.—Broken down gumma of the testicle.



Fig. 4.—Gumma of the testicle.

infiltration of lymphocytes and plasma cells between the tubules, proliferation of the fibroblasts of the stroma, thickening of the basement membrane and diminished spermatogenesis. The condition may be limited to small areas or may be generalized throughout the entire testis. In old severe cases the entire organ may become fibroid. Spirochetes can usually be demonstrated early in the process.

Gummata of the testicle, as stated above, are of later occurrence than interstitial orchitis, rarely being observed before the eighth to the tenth year. In one personal case a large broken down gumma of the testicle was seen 15 years after the chancre (see Fig. 3).

Gummata are rarely bilateral and occur as firm nodules of varying size, either single or multiple, enclosed in fibrous tissue. These may coalesce, developing into a large mass (even as large as an orange or larger) and may break down, forming fistulæ through the skin of the scrotum which develop into sloughing, ulcerating, necrotic sores. Histologically the typical gummatous areas are surrounded by a vascular layer of delicate, fibroblastic proliferation of the stroma, with considerable lymphocyte infiltration. Remains of the seminiferous tubules are observed between the gummatous areas.

CLINICAL HISTORY

Interstitial orchitis, as stated above, may be of such slight extent as to pass unnoticed and not be recognized except at autopsy. The condition is usually painless, of insidious onset and when recognized clinically is often done so only accidentally. On palpation the testicle is found of a very hard, wooden consistency. There is a gradual decrease in spermatogenesis and if bilateral a diminution of sexual desire. Rarely the development is more rapid with considerable swelling, pain, tenderness on palpation, redness and edema of the scrotum.

Gummata of the testicle as a rule give rise to few if any subjective symptoms. However, there is more or less pain and tenderness if the lesions attain any considerable size, and if both testicles are involved there is diminution of the sexual desire or even complete impotence depending on the extent of the process. Palpation reveals either a smooth or nodular enlargement, more frequently the latter.

DIAGNOSIS

Interstitial orchitis may be mistaken for traumatic orchitis or gonorrheal orchitis or epididymitis. In *traumatic orchitis* there is a history of injury and the development of the swelling is rapid, with pain, tenderness and redness of the skin.

Gonorrheal orchitis is a very rare condition, though epididymitis due to the gonococcus is very common. If the testis itself is involved it is almost always accompanied by an epididymitis which is not the case in syphilis of the testicle. In the gonorrheal condition also there are usually evidences of gonorrheal urethritis or a history of it.

Gummata of the testicle must be differentiated from tuberculosis and new growth. *Tuberculosis* nearly always begins in the epididymis and is more frequently and earlier associated with breaking down and the formation of fistulæ. In tuberculosis there is more pain than in gummata, while tubercle bacilli sometimes may be found in the discharge, which is thinner. Furthermore, the vas, seminal vesicles, and prostate more frequently show evidences of involvement.

Various types of *new growth* of the testicle have been described, but the majority of investigators nowadays ascribe a teratomatous nature to all. At any rate these new growths must be differentiated from gummata and this may present a great deal of difficulty.

New growths, as a rule, are of more rapid development than gummata and are more tender. Also they are more frequently accompanied by enlarged inguinal glands. Nevertheless it is often impossible to make a diagnosis upon the clinical findings alone. A history of syphilis or a positive Wassermann reaction would be strong presumptive evidence of syphilis, and, of course, a section of the lesion would settle the diagnosis at once. However, it is doubtful whether a biopsy is ever justifiable in this condition. It would therefore seem that in many cases the therapeutic test must be applied. If after two or three weeks of intensive antiluetic treatment there is no diminution in the size of the tumor, extirpation is indicated.

PROGNOSIS

The prognosis of syphilis of the testicle may be said to be good. That is, the process can be arrested in the majority of cases. However, the prognosis as to the function of the organs is not so favorable, although this depends entirely upon the extent of the process.

There is usually more or less atrophy but if the glandular elements have not been entirely destroyed the function may not be impaired. At least the patient may retain his sexual desire.

TREATMENT

The treatment of syphilis of the testicle is mainly specific, and arsenamine, mercury, and one of the iodides should be pushed vigorously. As long as the testicle is swollen a suspensory should be worn and in those rare cases of acute interstitial orchitis the patient should be confined to bed.

Gummata which have broken down and formed fistulæ should be treated locally. If the process is very extensive and marked suppuration exists, it may be necessary to remove the testicle.

EPIDIDYMIS

HISTORICAL

As pointed out above Astruc¹¹ was the first writer to mention syphilis of the testicle, and this astute worker apparently also was the first to recognize syphilis of the epididymis. He observed that tumors of the epididymis sometimes arose without the testicle participating in the process to the same extent.

While Benjamin Bell⁴ stated that the epididymis might share in the syphilitic process, he considered it always secondary to involvement of the testicle proper.

Sir Astley Cooper¹² also apparently believed that the involvement of the epididymis in the syphilitic process followed such involvement of the testicle.

Ricord,⁶ as stated above, admitted the possibility of syphilis of the epididymis, although he thought the process almost invariably affected the testicle.

Nelaton¹³ in 1852 reported 2 cases in which the epididymis was affected. However, it was Dron¹⁴ in 1863 who first called particular attention to syphilis of this organ. The author reported 16 cases in 14 of which the epididymis alone was involved to the exclusion of the testicle.

Since that time cases have been reported by Fournier,¹⁵ Zeissl,¹⁶ Balme,¹⁷ Pinner,¹⁸ Schadeck,¹⁹ Micheel,²⁰ Wright,²¹ Lisser and Hinman,²² Michelson,²³ and others.

FREQUENCY

Syphilis of the epididymis is not nearly as syphilis of the testicle proper, at least, the literature on the subject is comparatively meager. However, Klauder²⁴ states that since he has adopted the routine palpation of the testicles and epididymis of all syphilitics, "it has not been infrequent to note the presence of individual nodes in the epididymis of chronic syphilitics." This, also, has become a routine procedure with me and in a record of 276 syphilitics in which this has been carried out I have recorded the finding of small nodes in but three cases (one of these bilateral) and definite enlargement of the epididymis, but not nodular, in but three other cases. This gives a total of six cases of involvement of the epididymis in 276 syphilitics or about 2 per cent.

As stated above Dron¹⁴ observed 16 cases but the number of syphilitics examined is not stated, while Balme¹⁷ saw 13 cases in 2300 syphilitics.

PATHOLOGY

Syphilis of the epididymis occurs in three forms, an *acute* and a *chronic interstitial epididymitis* and *gummata*.

The *acute interstitial* variety may occur as early as the second month following infection (Zeissl), although as a rule it is of later occurrence, even as late as the fifth year of the disease. The swelling of the organ may be partial and nearly always begins in the globus major, but the whole epididymis may share in the process. The swelling, however, is not very great, although if the process is not checked distinct indurated areas develop which may attain the size of a small marble. A certain degree of hydrocele usually develops. While the condition is generally unilateral, both sides may rarely be involved. As far as I am aware the histological picture of this type of syphilitic involvement has not been described, but undoubtedly the swelling consists largely of an infiltration of lymphocytes and plasma cells, with hyperplasia of the fixed elements.

The *chronic* variety of interstitial epididymitis may follow the acute or it may develop without such an attack preceding it. It is of somewhat later occurrence, rarely being seen before the third year of the disease. As with the acute variety the upper pole is usually the seat of the beginning of the process, although in most cases the entire epididymis is involved to a greater or less extent.

It is usually unilateral. The swelling is rather diffuse with one or several more or less irregular indurations which may attain the size of a small plum. Fluid accumulates in the tunica vaginalis as a rule and may be of considerable amount, even as much as five hundred grams on each side (Wright). No description of the histology of this type of involvement can be found.

Gummata of the epididymis occur as a rule much later in the course of the disease than interstitial syphilitic epididymitis, although, according to Pinner¹⁸ earlier than gummata of the testicle proper.

Klauder²⁴ reports a case of bilateral gummata of the epididymis in a paretic whose syphilis must have been of a number of years standing, probably at least fifteen.

These lesions are usually multiple but rarely bilateral and vary in size from a pea to a hazelnut. Sometimes gummata of the epididymis are extensions from gummata of the testicle proper. Rarely these tumors break down and develop fistulæ forming ulcers with a thick, sticky discharge.

As with the other types of syphilis of the epididymis the histologic picture of gummata has not been described. However, Langhans²⁵ observed postmortem the gross section of a gumma of the epididymis. He states that it was a solid, caseous knot of angular, ramified shape about 1 cm. in diameter with a small transparent zone along the edges.

CLINICAL HISTORY

Acute syphilitic epididymitis usually begins rather suddenly with more or less severe pain, which is greatly increased on movement, making walking next to impossible. The swelling is not so great as one would expect from the pain. The surface of the epididymis is at first smooth and of an elastic consistency, exceedingly tender to pressure, and easily distinguishable from the testicle proper. Later, if the process is not checked, distinct indurated areas are palpable and in a few days the acute symptoms subside and a chronic course supercedes.

Chronic syphilitic epididymitis, if not a sequence of the acute type, is of slow, insidious development and usually is without pain. However, in a certain percentage of cases there is a dull, dragging pain in the scrotum and along the inguinal canal, which symptoms may

be the first to bring the patient to the physician. Palpation in the beginning reveals the epididymis hard and elastic, but later on it develops a board-like hardness, with irregular surface. As stated above, the process usually begins in the globus major but as a rule later involves the entire organ. Ordinarily pressure causes little or no pain, and the usual occupation of the patient is not interfered with. When the fluid in the tunica vaginalis is of considerable amount, it may entirely mask the condition of the epididymis and a diagnosis of simple hydrocele be made.

Gummata of the epididymis also are of insidious development and sometimes follow an injury. Palpation reveals one or more tumors of varying size which are smooth, hard and painless. There are no subjective symptoms.

DIAGNOSIS

Practically the only condition from which *acute* syphilitic epididymitis must be differentiated is *gonorrheal epididymitis*. The latter always begins in the globus minor while the syphilitic process nearly always starts in the globus major. In gonorrhea of the epididymis also there are nearly always other manifestations of gonorrheal infection, a urethritis or at least a history of such a condition and possibly involvement of the prostate and seminal vesicles with the finding of gonococci in the prostatic secretion. On the other hand, acute involvement of the epididymis in the syphilitic process is often accompanied by other early manifestations of this disease, syphilodermata, lesions of the throat and mouth, alopecia, etc. Also the Wassermann test is likely to be positive.

Of course it must be remembered that syphilis and gonorrhea are not infrequently associated in the same individual and in certain cases it may be necessary to resort to the application of antiluetic therapy to clear up the diagnosis.

Chronic interstitial epididymitis due to syphilis may be mistaken for *gonorrheal* epididymitis or *tuberculous* epididymitis. Practically the same points as have been mentioned in the differentiation of acute syphilitic epididymitis and gonorrheal epididymitis apply to the differentiation of the chronic type from gonorrhea of this organ.

The differentiation of chronic syphilitic epididymitis and tuberculous epididymitis may be most difficult. However, in the latter there is a much greater tendency to soften and the formation of fis-

tulæ. Also the vas, seminal vesicles and prostate, are more frequently involved than in the syphilitic condition.

Gummata of the epididymis may be mistaken for *tuberculosis* or *new growth*. In the former condition the differentiation depends upon the same factors as just mentioned under chronic syphilitic epididymitis.

New growths of the epididymis are similar to new growths of the testicle proper and in their differentiation from *gummata* the same may be said as was mentioned under *gummata* of the testicle.

Finally, in the diagnosis of syphilis of the epididymis it may be said that the history, the presence or absence of other manifestations of syphilis, including the Wassermann test, and the result of anti-luetic therapy are probably of more importance than the findings in the epididymis, itself.

PROGNOSIS

The prognosis of syphilis of the epididymis is good, as most cases clear up rapidly under specific therapy, although a certain amount of induration may remain for many months.

TREATMENT

The treatment of syphilis of the epididymis is the same as treatment of syphilis of the testicle proper.

SPERMATIC CORD

INTRODUCTION

Syphilis of the spermatic cord undoubtedly is of rare occurrence. In a careful search of the literature references to only 13 cases purporting to be this condition can be found.

The early syphilographers apparently did not recognize syphilis of the spermatic cord and no mention of it can be found in the writings of Astruc, Hunter, Bell or Ricord.

HISTORIC AND CRITICAL REVIEW

OBSERVATION I, HÉLIOT,²⁶ 1846

The first reference to involvement of the spermatic cord seems to be by Héliot in 1846. He reported 2 cases of syphilis of the testicle in one of which (Obs. II) he states the cord was three times the normal size but presented no lumps and upon strong pressure the patient felt a little pain.

In the second case (Obs. III) the cord was double the normal size without any lumps and pressure produced no pain.

The evidence in these cases is so meager that they cannot be accepted as cases of syphilis of the spermatic cord.

OBSERVATION II, LHONNEUR,²⁷ 1856

The patient gave no history of syphilis. The tumor started August 16, 1855, without any known cause. It developed in two months and on the 18th of October was the size of two fists, hard, lardaceous, and extended as far as the iliac fossa. The pain was dull with exacerbations. The patient was given 5 pills of hemlock of .05 centigrams. The tumor diminished then under the influence of the treatment or by a simple coincidence and became the size of a small egg. However, he died in December from cerebral hemorrhage. At autopsy the right testicle was normal. The cord appeared infiltrated in a large fatty mass, and an accumulation of fibers.

Microscopically Verneuil recognized a gummy tumor. A gummy tumor the size of an egg was also found in the right auricle.

This was undoubtedly a case of syphilis of the spermatic cord and is therefore the first authentic one to be reported.

OBSERVATION III, LANCEREAUX,²⁸ 1873

A patient of forty, who had had syphilis for eight years presented himself with a tumor of the scrotum the size of an adult fist. The right spermatic cord formed a hard, rigid rod as big as a finger, enlarged at several points, one of which was the size of a large chestnut. This condition had begun to develop five years previously and for one year had been the seat of shooting pains. Under potassium iodide the spermatic cord was reduced to the size of a quill and became more supple.

In all probability this was a case of syphilis of the spermatic cord and is accepted as such.

OBSERVATION IV, DESPRÉS,²⁹ 1875

On February 3, 1875, Després reported before the Surgical Society of Paris three cases of syphilis of the testicle in infants, which had been observed by Obidinare in the hospital at Bucharest in one of which the spermatic cord was as large as the thumb of the child.

The evidence in this case is too meager upon which to base a diagnosis of syphilis of the spermatic cord. It is therefore not accepted.

OBSERVATION V, RECLUS,³⁰ 1882

Reclus observed two cases of testicular syphilis in which the vas deferentia were stiff and rigid as a glass rod and the size of a penholder.

The insufficient evidence in these cases does not warrant their acceptance as ones of syphilis of the spermatic cord.

OBSERVATION VI, ZEISSL,³¹ 1883

N. Gustav, twenty-five years old, was seen on the ninth of December, 1882. His syphilis dated from April, 1882, and was first seen in the clinic August 25, 1882. At that time he had a maculopapular syphiloderm, mucous patches on the anus and upper lip. By the use of potassium iodide these lesions disappeared by the eighteenth of September. On December 9, 1882, he returned with moist papules on the penis and scrotum, papules on the forehead and lower lip. He received 2 grams of potassium iodide daily and three days later there was observed on the right seminal duct a massive thickening which increased rapidly in size until the eighteenth of December there was found in the scrotum an irregular swelling the size of a pigeon's egg which was flattened and irregular. It was elastic and with the exception of the lower pole was nodular. There was no pain on pressure, but pressure seemed to cause the swelling to go down and as though a ridge separated it into two parts. The testicle was distinct and free under the swelling. There was no transparency. The vas could be distinctly felt on the external surface of tumor. From the upper border of the tumor the seminal duct was found thickened to the external ring. A diagnosis of syphilitic new growth was made and on January 9th the tumor, which was the size of a hen's egg and which contained about 100 grams of pus, was removed. The patient was put on antiluetic treatment and by February 18 the cavity was completely healed, while on the twelfth of March he was discharged as cured.

This case was apparently one of syphilis of the spermatic cord and is so accepted.

OBSERVATION VII, BERT,³² 1889-91

M. Z., aged thirty-one, presented himself to the clinic March 30, 1887, for multiple tumors of the two spermatic cords. At the age of eighteen the patient had had a chancre, probably indurated, but denied a roseola and the other ordinary symptoms of syphilis. For that reason he had not been treated, and five years later he had married. His wife had had three pregnancies, the first terminated in an abortion in the fourth month, the second in the seventh month, and the third resulted in a living child born at term, but very puny and it died after about one month. About four months prior to the examination, the patient had been aware of hard and indolent tumors in the two spermatic cords, which had enlarged very rapidly and had remained stationary since that time. Painting with iodine had resulted in no change. Examination revealed the two testicles a little enlarged but regular, of normal consistency, and their sensibility to pressure was preserved. The two epididymes were healthy. The cords in the inguinal canal appeared in no wise enlarged or indurated, but in the scrotal portion they presented curious tumefactions.

On the right side there were found two tumors, the one situated just at the entrance of the inguinal canal, the other about one centimeter underneath. The first was the size of a large cherry, the second very small. Both were very regu-

lar on their surfaces and their consistency was extremely hard and inelastic. The skin was shiny over them, but not edematous and on movement of the deep tissues they appeared to grow with the elements of the cord. On the left side examination revealed the existence of two superimposed tumors, but a little different in their location and disposition. The upper one was very small and was a good fingerbreadth beneath the orifice of the inguinal canal. The under one was placed at the height of the epididymis where it was perfectly distinct. The two left tumors were of the same regular character and consistency as the right tumors. In the canal of this side there was a little liquid. Rectal examination revealed the prostate and seminal vesicles normal. The bladder was healthy and the urine normal. There was no functional trouble in the urinary or genital organs.

M. Prousson did not make a positive diagnosis at first and he hesitated between a tuberculous infiltration and a gumma of the cord. He leaned particularly toward the second hypothesis on account of the past history of the patient and the successive abortions of his wife. Consequently he advised the application of the plaster of Vigo to the tumors and the administering of a general mixed treatment, mercury rubs and potassium iodide internally.

On the 21st of June the patient presented himself again to the clinic. He had followed exactly the treatment prescribed without obtaining the least modification in the condition of the tumors. They presented themselves with the same characteristics as on the first visit.

The treatment was replaced by the sirup of Gilbert, but the patient obtained no result so abandoned it.

However, the tumors of the cord remained stationary, without alteration of the skin, according to the patient.

One day in September, 1887, while walking, the patient felt himself "very much inundated" and upon returning home much to his surprise he found the large tumor on the right side had opened at the superior part of the scrotum near the groin. From this small opening there escaped a grumous, milky fluid. Pressure caused more of the fluid to exude and the small lower tumor presented itself in the same. During many months the fistula remained open and continued to give forth a serous, grumous fluid without any local reaction. At the finish, however, the flowing stopped. While the phenomena which have just been described were taking place in the tumor of the right cord, the left one also underwent a most remarkable modification. Without any opening to the exterior, without traces of reaction, it diminished insensibly to almost nothing and finally reduced to a trace which was verified then and at a later examination of the patient.

While the above case was diagnosed as gummata of the spermatic cords, it seems that if it had been, the tumors would have diminished in size under the specific treatment administered. It, therefore, is not accepted.

OBSERVATION VIII, FULLER,³³ 1893

In a patient who had contracted syphilis some years previously Fuller observed the appearance of a painless, quite firm tumor, which attained the size

of an almond, in connection with the cord of the left side, just outside of the external ring. Under mixed treatment this soon disappeared.

Although the details of this case are not given by Fuller, it seems that there is enough evidence to justify a diagnosis of syphilis of the spermatic cord, and the case is therefore accepted as such.

OBSERVATION IX, SAVINSKI,³⁴ 1899

A man of twenty-four, a soldier, unmarried, entered the clinic October 23, 1898. He had never been seriously ill, but in the middle of June there was a sudden swelling of the left testicle with great pain. He denied syphilis. Examination revealed enlarged left inguinal glands and the left half of the scrotum two or three times the size of the right which was normal. The left half was translucent, and the tumor was evidently due to the accumulation of fluid in the tunica vaginalis. There was apparently no difference in the tumor when the patient was lying down and the condition was diagnosed a hydrocele. Gonorrhea was denied and none was found. In the head of the right epididymis was clearly felt a globule the size of a hazelnut, cartilaginous in consistence, while the right testicle was normal. In the head of the left epididymis and in the body of the testicle two balls were clearly felt of the consistence of lime, each the size of a hazelnut. Slightly above these two, 1.5 to 2 centimeters along the course of the spermatic cord, a third ball was felt, smaller than the other two, but of the same consistence and similar in contour. The left vas deferens was adherent to the epididymis, while the right was free. There was no pain, but on pressure the right was more tender. There were no alterations in the prostate or the seminal vesicles. Savinski excluded cancer, sarcoma and tuberculosis by the symptoms, physical signs and history, and concluded that the patient had syphilis of both epididymis, left seminal cord and left testicle, the hydrocele being a sequel.

Treatment: From October 24 to November 13 hot compresses were applied to the testicles followed by mercury plasters. Potassium iodide was administered internally 3 grams per day. Mercury salicylate 0.06 grams was also injected intramuscularly, beginning on November 14th. After the fourth injection improvement was prompt, the nodules in the left epididymis were reduced in size and in the spermatic cord vanished.

There seems no doubt but that this was a case of syphilis of the spermatic cord and is therefore so accepted.

OBSERVATION X, GOLDENBERG,³⁵ 1901

A young man, twenty-three years of age, came under Goldenberg's care at the Mount Sinai Hospital Dispensary on account of syphilis of six months' standing. He had been free from all manifest symptoms when he presented himself one day with a swelling on the left side of the scrotum, which he discovered accidentally, and which was not due to any traumatism.

On examination, there was found on the left posterior surface of the scrotum, about $\frac{1}{4}$ -inch from the raphe, around, sharply circumscribed, hard mass, slightly

cystic in feeling, about 2 cm. in diameter, giving a sense of fluctuation to the examining finger. The tumor was slightly adherent to the skin, which did not show any visible changes in color or structure; there was no spontaneous pain, but tenderness on pressure. Testicle and epididymis were absolutely normal, the spermatic cord otherwise unchanged.

Goldenberg had the impression that the tumor originated from the cord, and that he had to deal with a gumma of the latter. Dr. Lockett, however, thought that the tumor was free from the cord and was inclined to consider it a sebaceous cyst.

His suggestion to make an incision was carried out, and the mass was found to be adherent to the skin by inflammatory exudate and closely connected with the cord. It was not as sharply circumscribed as it had appeared to be from the external examination, and it had extended somewhat into the surrounding tissues. The tumor proper had the characteristic bluish-gray appearance of a gumma, and in several places showed evidences of breaking down.

Although the correctness of the diagnosis of gumma of the spermatic cord was undoubted, a piece was excised for microscopic examination which was done by Dr. Mandlebaum, the pathologist of the Mount Sinai Hospital.

His report is as follows: The section shows areas of speroidal cells of uniform size, in the middle of which there are numerous blood-vessels, many showing a mild degree of endarteritis, others being entirely occluded (endarteritis obliterans). In other places a moderate and dense network of newly formed embryonal connective tissue with hyaline changes is noted. Quite a large number of newly formed capillaries are seen in these areas, which give the impression of a succulent fibrous growth. Parts of the section are invaded by a mass of leucocytes and fibrin, showing that an inflammatory process had been present. No giant cells are to be seen. Diagnosis: Gumma with secondary inflammatory changes.

There can be no doubt of the correctness of the diagnosis in this case and it is the first and only one reported in which the microscopic picture is given.

OBSERVATION XI, CAMPBELL,³⁶ 1901

C. S. presented himself for treatment in 1897, with a history as follows: In the fall of 1890 a sore appeared on the right side and about the middle of the shaft of the penis four weeks after intercourse, followed by enlarged glands, chainlike in character, affecting only the right inguinal region. There was no pain or tenderness on pressure, and this was followed by a roscolar eruption. Early in 1891 mucous patches appeared in the mouth and on the fauces. In 1897, when the patient came under Campbell's care, he complained of pain and tenderness along the left tibia from the knee down to the ankle, the pain becoming intensified at night. On the right foreleg five ulcerating gummata presented, kidney-shaped, with undermined edges, and emitting considerable serous discharge. The ulcers had existed for about nine months, and promptly healed under the potassium iodide treatment, but as usual in these cases the patient then disappeared. In August, 1899, he again presented himself with a firm painless tumor, about

the size of an almond, presenting just outside the external ring, in connection with the cord of the right side. This promptly disappeared under the iodide treatment and inunctions of vasogen mercury, 33 per cent, since which time no further syphilitic manifestations have been noted.

There seems to be no doubt but that Campbell's case was one of syphilis of the spermatic cord.

DISCUSSION

INCIDENCE

Only 13 cases purporting to be syphilis of the spermatic cord have been reported in the literature. Of these 13 cases, 7, or about 54 per cent, are accepted as authentic.

No case of undoubted involvement of the spermatic cord in the syphilitic process has come under my observation, but recently I saw in the practice of one of my colleagues a case which was possibly such. In this case a man of about 40, who gave a history of chancre eight years previously, and at the time of observation had a number of ulcerating gummata of the legs and a positive Wassermann, presented a tumor the size of a hickory-nut in the left spermatic cord. As this man did not return for treatment, I did not have an opportunity to observe the effect of specific therapy, so it is not included in this study.

It is apparent from the above that this type of involvement is a rare condition. Of the 13 cases 8 were reported in the French literature, 3 in the American, and one each in German and Russian literature.

ETIOLOGY

Stage of the Disease.—Of the 7 cases of syphilis of the spermatic cord which have been accepted as authentic, the length of time following syphilitic infection is definitely stated in four and was respectively six months, eight months, eight years and nine years. In Fuller's case it is stated that the condition developed "some years" after infection. In Lhonneur's case there was no history of syphilis and Savinski's patient denied such infection.

Age.—The age of the patient is given in 4 cases and was respectively twenty-three, twenty-four, twenty-five and forty years.

PATHOLOGY

The gross pathologic condition in all of the cases was one of enlargement, and the size varied from mere "thickening" to a tumor as large as two fists. In 4 of the cases the enlargement was on the right side and in 3 on the left side.

In only 1 case (Lhonneur) are the postmortem findings recorded. In this case it is stated that, "the cord appeared infiltrated in a large fatty mass, and an accumulation of fibers," and that microscopically it was recognized as a gummy tumor.

In 1 case (Goldenberg) the histologic picture following excision is given in detail and has been recorded above.

CLINICAL HISTORY

The length of time required for the development of the condition is recorded in only 2 cases, in 1 of which (Lhonneur) it was two months, while in the other (Lancereaux) it was five years.

Pain in Lhonneur's case was recorded as of a dull character with exacerbations and in Lancereaux's case shooting pains were observed. In Goldenberg's case there was no pain, but there was tenderness on pressure. The remaining cases were recorded as painless.

In 2 of the cases the consistency of the tumor was recorded as hard and in Savinski's case the consistency was recorded as that of lime. The consistency of the tumor in Zeissl's case was recorded as elastic and in Fuller's case as quite firm. In the remaining cases the consistency is not recorded.

Other symptoms are not mentioned.

DIAGNOSIS

Syphilis of the spermatic cord must be differentiated from other tumors of this organ, such as fibromata, sarcomata, and lipomata and tuberculosis, and as there is nothing pathognomonic of the condition, the diagnosis must depend upon the history, the presence or absence of other symptoms of syphilis and the result of specific therapy.

PROGNOSIS

The prognosis of syphilis of the spermatic cord is good. In 4 of the authentic cases the tumors disappeared under specific therapy and in 2 others they were reduced in size, while in Goldenberg's case the tumor was excised.

TREATMENT

The treatment of syphilis of the spermatic cord is entirely specific and consists of the administration of arsphenamine, mercury, and one of the iodides.

SEMINAL VESICLES

That the seminal vesicles may be involved in the syphilitic process has never been shown. Most writers on syphilis either ignore the subject entirely or pass over it with a remark that syphilis of the seminal vesicles is rare. There seems to be no reason, however, that these organs should be exempt from attack by the *Spirocheta pallidum*, and undoubtedly if the seminal vesicles of all syphilitics who come to autopsy were carefully examined, evidence of involvement would sometimes be found.

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REPORT OF A CASE OF SYPHILITIC ULCERATION OF THE
VAGINAL VAULT AND CERVIX COMPLICATING PREG-
NANCY AT THE EIGHTH MONTH, CURED BY ANTI-
SYPHILITIC TREATMENT AND FOLLOWED
BY NORMAL LABOR AT FULL TERM

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P. B., COLORED, age seventeen, (Grady Hospital No. 1442), was admitted to the hospital Dec. 12, 1919, with a diagnosis of irregular bleeding due to placenta previa. Her menstrual history was normal and the last period was said to have occurred in May, the exact date of which she could not remember. She had been married nine months and previous to this time had always been in good health. She gave no history of specific symptoms.

The pregnancy had progressed normally up to about the middle of November, when, at about the seventh month, she began to have a foul leucorrheal discharge. About two weeks later this became associated with irregular bleeding requiring about two pads a day, but without any profuse flow or clots. A physician, called to the house, made a diagnosis of placenta previa and sent the patient to the hospital.

Examination showed the patient to be of small build. The skin was clear and free from eruption or scars. The throat was negative and there was no general adenitis. The heart, lungs and blood pressure were normal. The fundus reached to within three finger-breadths of the ensiform, corresponding to about eight months gestation. The child presented normally and the fetal heart sounds were distinctly heard. The pelvis was of the generally contracted type.

Vaginal examination showed no external scars or ulcers and no laceration. There was a thin, foul, grayish, blood-tinged discharge.

The lower part of the vagina was normal but the entire vaginal vault was apparently converted into one large circular ulcer about 3 cm. in diameter. The borderline between normal and diseased vaginal wall was marked by a well-defined circular rim of gristly tough tissue which could not be broken off or removed with the finger. Within and above this rim on all sides, the finger passed around and up into a cavity evidently formed by necrosis, the surface of which was roughened and sloughing but not cauliflower or friable as cancer. Just beyond the first circular opening and at the upper end of the cavity was a well-defined, small, soft, slightly projecting structure with an opening which admitted the finger tip and through which the smooth membranes and fetal head could be felt. No placental tissue could be reached. Apparently the process involved principally the vault and affected merely the superficial portion of the cervix. Several pieces of tissue were removed from the diseased area and had to be forcibly twisted off and pulled away with forceps. There was no more than a slight amount of bleeding from these manipulations. A sample of the patient's blood and a piece of tissue in 10 per cent formalin were sent to Dr. Ayers at the hospital laboratory and to Dr. J. Funke for examination. While waiting for these laboratory reports, the patient was given a 1 per cent lysol douche three times daily to clear up the secondary infection as rapidly as possible, in case labor should begin earlier than expected.

Several days later both laboratories reported the Wassermann to be four-plus and the tissue to show changes indicative of syphilis, such as fibrosis, increased vascularity, with marked small round-cell infiltration about the vessels. No giant cells, tubercles or evidences of cancer were seen.

The patient was accordingly put upon intensive antisyphilitic treatment consisting of intravenous injections of neodiarsonol in 0.6 gm. doses at intervals of five or six days; intramuscular injections of mercuric salicylate gr. 1, at weekly intervals and daily inunctions of mercuric ointment, receiving in all four intravenous and three intramuscular injections along with daily douches and inunctions. There was considerable improvement from the douches during the few days they were given alone, but the improvement was most rapid and satisfactory after the antisyphilitic treatment was commenced. Examination at intervals of several days showed the ulceration rapidly filling in and softening to such an extent that on examination

two days preceding the onset of labor, there remained merely the lower softened margin of the original ulcer. The discharge and bleeding had entirely disappeared and the cervix was so nearly normal that the prognosis for natural dilatation appeared to be good.

Premature rupture of the membranes occurred the evening of Jan. 6, 1920, about four weeks after admission to the hospital and was soon followed by the onset of pains. The head remained at the inlet about thirty-four hours in spite of frequent severe pains, but this delay was apparently due more to the generally contracted pelvis than to the condition of the cervix and vaginal vault, for the latter softened and dilated satisfactorily during this time.

After sufficient molding of the head, progress became rapid and a normal appearing female child, weighing six pounds, was delivered spontaneously. It showed no evidence whatever of disease, although a sample of blood taken from the cord showed a two-plus Wassermann. There was no more than the normal amount of bleeding during and following the delivery, and the placenta showed nothing unusual in appearance.

Both mother and baby were treated by inunctions during the following two weeks in the hospital, at the end of which time a Wassermann test on the mother was found to be negative. During this time the husband's blood was tested and a four-plus Wassermann obtained. He gave a history of primary sore in June, 1918, for which he had received some treatment while in the army.

A pelvic examination made two weeks after delivery showed a slight bilateral laceration of the cervix with a moderate amount of scar tissue at the left angle somewhat blending together the cervix and vaginal fornix on that side, but not much more evidence of injury than is frequently found in normal cases.

Abstract of Current Syphilis Literature

It is the purpose of this JOURNAL to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Wm. H. Deaderick, Dugan-Stuart Bldg., Hot Springs, Arkansas.

WM. H. DEADERICK, M.D., EDITOR

NASAL SYPHILIS. WITH CASE REPORT.—A. Wade Thrasher. Indianapolis Medical Journal, 1920, vol. xxiii, No. 1, p. 5.

The author emphasizes the part played by syphilis in the etiology of certain obscure nasal conditions, as in the case of a man thirty-four years of age who complained chiefly of nasal stenosis and hypersecretions of the left nasal fossa with neuritis over the left frontal and temporal regions. The nose was normal except a marked swelling or tumefaction of the septum superiorly, and there was no sinus involvement. Notwithstanding the negative personal history and the absence of concomitant symptoms, the author suspected this to be a gummatous infiltration of the septum, and placed the patient on progressive doses of potassium iodide, for observation. The induration and swelling of the septum along with the excessive discharge and neuritis disappeared so rapidly under this treatment that he was led to suspect this septal condition was precocious periostitis or syphilitic periostitis, instead of gumma. A Wassermann test was made and the report showed positive 4+. The diagnosis of this condition might have been easily overlooked, especially in this stage, in the absence of concomitant symptoms and negative personal history. Syphilitic nasal lesions have been mistaken for sarcomata and epitheliomata, and a supposed hyperostosis of the septum has been proved by later developments to be gummatous growth. In the interest of early clinical diagnosis, the author points out the importance of confirmatory bacteriologic examination in doubtful cases.

SYPHILITIC HEMIPLEGIA.—O. E. Adorni. La Semana Medica, 1919, vol. xxvi, No. 34, p. 211.

The author reports a case of hemiplegia of syphilitic origin in a man twenty-nine years of age. The onset was abrupt, without prodromata of any kind, in the form of a crossed hemiplegia which attacked

the right arm and leg, and the opposite side of the face. A cure was obtained by means of specific treatment, exclusively, the conclusion having been reached that syphilis was the only cause which could give rise to the manifestation in this instance. The process was referred to a syphilitic lesion of the vessels, as suggested by the age of the patient, the insidious and rapid onset of the hemiplegia, the enlargement of the liver and spleen, the exostosis of the right tibia, and the roughening of the elbows and shin bones. On the basis of these data, treatment was instituted in the form of one daily intramuscular injection of biniodide of mercury 0.02 ctg. in water solution. Improvement was experienced following the fourth injection, with subsidence of the arthralgias and bone pains, and especially of the severe headaches which had yielded to no analgesic remedy. It is a common and practically constant observation that the headaches are frequent and extremely severe in syphilitic arteritis of the cerebral vessels, culminating in paroxysms of pain not to be controlled by morphine. The patient suffered from these headaches, which were undoubtedly due to syphilitic arteritis. Vascular rupture occurred insidiously, as a slight extravasation, which later on rapidly increased and gave rise to the hemiplegia for which the patient came under treatment. Up to twelve daily intramuscular injections of 0.02 ctg. of biniodide of mercury were administered, and after an interruption of fifteen days, another identical series was given. Next, after one month's rest, injections of gray oil were started (one weekly, of 8 drops), with forty drops daily of potassium iodide. Improvement manifested itself from day to day, with prompt return of speech, movement, and ability to walk.

A TRAUMATIC NEUROSIS IN A CASE OF SYPHILIS—CASE REPORT.—James A. Wynn, Indianapolis. *Indianapolis Medical Journal*, 1919, vol. xxii, p. 570.

The existence of a four-plus Wassermann should not blind us to the fact that an entirely independent nervous lesion can co-exist with syphilis. In this case, the faulty verdicts of two hospitals did real harm in focusing the patient's attention on a wrong conception of his condition, and the cure of his neurosis was impeded by his well-established belief that he had incipient taboparesis.

OBSERVATIONS ON CONGENITAL SYPHILIS.—Ellen M. Kent Hughes, Brisbane, Australia. *Medical Journal of Australia*, 1919, vol. ii, p. 329.

The ages of the patients varied from three weeks to eight or nine years. The most strikingly successful cases have been those of breast-fed babies with skin lesions. Most of the syphilitic infants

look healthy when born and if they are breast-fed and treated immediately the lesions appear, they do well. Artificially-fed infants have been very difficult to treat and most of them die of gastro-enteritis. However, it must be remembered that they were all admitted to hospital for that complaint and the syphilitic condition was discovered afterwards. The skin lesions amongst the infants have varied considerably. One baby three weeks old was covered from head to foot with scaly circinate sores resembling rupiæ; they cleared up completely after two injections. Others had scattered papules and macules on the body and intense erythema of the buttocks. The commonest lesions were peeling macules of fingers and toes and buttock rash. Many children had snuffles. The older children, as a rule, have been well developed and have none of the classical stigmata, such as saddle-back nose, Hutchinson's teeth, frontal bossing, etc. They have been suffering generally from one special manifestation of the disease and because they look healthy, their condition is undiagnosed. Several apparently perfectly healthy children whose serum yields a positive Wassermann reaction, are being treated, as their brothers or sisters have various lesions. We have had four cases of troublesome glossitis, all associated with positive Wassermann reaction; three appeared otherwise healthy, the fourth was sent in with myocarditis and had been three months in bed. There have also been two cases of delayed dentition and one of caseation and infiltration of the cervical glands and necrosis of the nasal bones. Another child was admitted partially paralyzed with meningitis. Two children with strabismus gave a positive Wassermann reaction. In one the disease was congenital and in the other the symptoms had only been noticed for four months. A positive Wassermann reaction was obtained in all the older children, but some of the obviously syphilitic infants gave a negative response to the test. In two of these cases I tested the mother's blood and found a positive reaction. On the other hand, the serum of the mothers of several syphilitic infants gave negative results. The author uses either novarsenobenzol or neokharsivan, as they cause less inflammation than arsenobenzol or kharsivan. For injection an ordinary syringe is used with a moderately large needle. The injection sites chosen are the outer and upper quadrant of the buttocks and under the pectoral muscles. Each week a different site is used. Six weekly injections are given. For infants under one year the dose is increased by 0.01 gm. each injection. For children under six years the dose is increased by 0.02 gm. and over six years by 0.03 gm. each injection. Mercury in the shape of hydrargyrum cum creta orally, or collosal hydrargyrum by injection is administered together with the arsenical preparation.

RADIOGRAPHIC DIAGNOSIS OF PULMONARY SYPHILIS.—*Deutsche Fortschritte a. d. Gebiete der Roentgenstrahlen*, 1918-19, vol, xxiv, p. 6.

The diagnosis of syphilis of the lung is not yet very reliable, so that the following instructive observation will prove of general interest. The patient was a clerk, 26 years of age, who complained of dyspnea, cough, and fever; hematemesis was claimed to have occurred a few times. Radiographic transillumination showed a blurred pulmonary apex anteriorly on the left side, shadows over both apices posteriorly. Individual spots in the right lung. Well-marked hilus design. On the left side, corresponding to the boundary of the two lobes, dorsoventral transillumination showed a deep band-like shadow passing upwards, with its base turned towards the hilus and its apex towards the periphery. Downwards the lower portion of the lung was blurred and shadows were seen over the left heart as well as over the diaphragm which was not freely movable. The mediastinum was free, and the aorta shadow was not enlarged. No inspiratory displacement of the mediastinum into the normal half of the thorax could be demonstrated on sagittal transillumination. Tubercle bacilli were not found in repeated examinations. The Wassermann reaction was positive. Mercurial treatment was followed at first by improvement, but later on by an acute aggravation. Under extremely distressing attacks of coughing, somewhat offensive masses of greenish mucus were suddenly expectorated from the deeper air passages, and the inspiratory stridor visibly diminished. Considerable dyspnea persisted after this attack, the voice becoming hoarse, and the breathing was shallow. Higher temperatures now made their appearance. The radiographic findings at this time were somewhat different. The previously solid central shadow on the left lung now presented areas of focal lightening at the base, so that its first portion assumed a reticular structure, while the rest of the findings remained approximately the same. The patient died. According to the autopsy findings, the radiographs had to be interpreted as follows: The peculiar configuration of the wedge-shaped central shadow corresponded to the dense pleuritic scar tissue together with the thickened bronchial walls and the cavities filled with secretion. When a part of the secretion in these cavities was voided by coughing, under the influence of treatment, this shadow began to clear up. Through its situation at the level of the pulmonary affection along the lowest segments of the upper lobe and the highest segments of the lower lobe, the shadow yielded a picture resembling an interlobar exudate. The chief distinctive features are represented by the form of the shadow and the turning of its base toward the hilus. This shadow-configuration is apparently characteristic of the most frequent form of pulmonary syphilis in adults, namely,

the chronic intermittent form with bronchiectases, and may prove of value in the rendering of the diagnosis. As the pleural affection usually develops at an early stage at the level of the pulmonary scar and cicatricial tissue, treatment may still be advantageously instituted when the process is recognized at this time by means of radiography.

CONDITIONS OTHER THAN LUES GIVING POSITIVE WASSERMANN.—M. O. Biggs, Fulton, Mo. *Journal of the Missouri State Medical Association*, 1919, vol. xvi, p. 326.

Wassermann reactions were begun on all patients in State Hospital No. 1, Fulton, Mo., as a routine measure about four years ago and during that time attention has been drawn to the large percentage of hyperthyroid cases giving a positive Wassermann in which the observers were unable either from clinical history, physical examination or inquiry into the family records, to establish any syphilitic infection or taint. It is a well known fact that goiter is much more prevalent among women than men, and their experience has been no exception to the rule. The patients of whom the author writes are insane, with two exceptions, and have been diagnosed under the head of thyrogenous psychosis, all of whom became unmanageable to a greater or less degree at their respective homes, necessitating their confinement in an institution for the insane. The psychosis of each, in the main, is characterized by wild delusions, irritability which sometimes develops into acute excitement, slow speech and deliberate mentation, absence of suicidal or homicidal tendencies, lassitude and indifference to surroundings, and apparent feeble-mindedness in some. We find in these cases a total lack of the symptoms which are manifested in a psychosis which results from luetic infection, either acquired or inherited. The physical signs are such as one would find in the average case of this type. In most of the cases an exophthalmic state was found to exist with marked tachycardia and other symptoms which accompany conditions of this kind. In some of the cases the enlargement is more lateral and varies in size to a great extent. The changes in the skin, teeth, blood, and temperature of the body are typical of this class of cases. The number of thyrogenous cases to which the author calls attention is twelve: all these cases are positive Wassermann. The prevailing mental tone associated with the disease is fear and apprehension, frequently associated with hallucinations of hearing and vision; voices may be heard saying disagreeable things and with these hallucinations occur anxious and agitated states. A few cases of acute thyroidism, with active delirium, are occasionally seen following operations on the gland, and may be due to the expression of its secretions by handling it and subsequent absorption.

SOME OBSERVATIONS ON THE DISCREPANCIES AND STANDARDIZATION OF THE WASSERMANN TEST.—Guy Hollister, Spokane, Washington. *Northwest Medicine*, 1920, vol. xix, p. 21.

While with the Laboratory Division of the American Expeditionary Forces the writer conducted 5000 Wassermann tests, using the reagents as standardized and sent out to the various laboratories by the Medical Department Central Laboratory. The standard technic that was adapted by the Division of Laboratories was also employed. A monthly supply of antigen and antishoop amboceptor was received for a period of twelve months. The amboceptor supplied was in every instance labeled, giving the approximate titrated values, the dilutions and the exact amounts to be used in the test. This reagent was found to be uniformly satisfactory and in almost every instance a check titration would reveal the approximate titer as indicated on the label. The antigen extract, as standardized and sent out by the Medical Department Central Laboratory, was an alcoholic extract of beef heart, containing cholesterolin to one-half saturation and was also labeled with the dilutions and amounts to be used. The antigens furnished were found to be the source of the greatest variation in the test, as evidenced by the results obtained when antigens from two different months' supplies were employed in making a series of a few hundred tests. In one instance an antigen that was supplied for the month of July, 1918, when run in comparison with an antigen furnished for the month of August, 1918, with 415 sera, gave twenty-five positive reactions, as compared with ten positive reactions obtained with the antigen furnished for the month of August, a discrepancy of 60 per cent between the two antigens, the newer antigen being the least sensitive. In another instance, in comparing antigens supplied in three different months by the Medical Department Central Laboratory with an antigen prepared and standardized in their own laboratory, that had been in constant use for more than six months, and by repeated titrations showed no deterioration in its antigenic properties, gave from 25 to 75 per cent more positive reactions than did the three antigens supplied by the Medical Department Laboratory. The Wassermann test in every case was compared with the history and clinical findings and in only one instance did the Wassermann show positive in the absence of a history and clinical findings, which upon repeated re-examinations gave negative reactions. In four cases of secondary syphilis in the florid state, two different antigens supplied failed to give a positive reaction in any degree. One antigen had been recently standardized and sent out. Using the more sensitive cholesterolinized antigen two cases were observed that gave eight to ten negative reactions in a period of ten to twelve weeks after the appearance of the initial lesion, and almost at the same time secondary symptoms and a positive Wassermann were

observed. In reviewing the literature and the results obtained by different workers, there can be no doubt that the quality of the antigen extract determines that of the results obtained and, until a uniform source and method of preparing this reagent is established, the results of different workers must differ in a certain proportion of cases. It is not so much in frankly negative or strongly positive serum that this happens as in an important class of what may be described as border-zone sera. These are provided by primary, latent and well treated cases of syphilis, in which the reaction to the most delicate methods is not strong.

ON THE SERUM-DIAGNOSIS OF SYPHILIS.—Frederick C. Lewis, Liverpool. *Lancet*, London, 1920, vol. cxcviii, p. 11.

An attempt was made to standardize the red cell suspension by the estimation of liberated hemoglobin by means of a clinical hemoglobinometer, but this method was ultimately abandoned, principally owing to the error inevitably introduced in the final color-matching. With the adoption of the "relative weight method" a standard suspension is obtainable, in which the errors due to making up the percentages and the possible large errors introduced by variations in centrifugalization are eliminated. It may perhaps be justly claimed that this method of standardization of the red blood cell suspension will give a practically unvarying concentration of red cells for every series of tests, and will establish a standard value for the term "minimum hemolytic dose" of complement. It is not claimed that this method of standardization is any considerable advance in technic because many thousands of excellent results have been obtained without it. The previous lack of such a standardization may, however, partly explain the known differences which exist between the results obtained on the same serum by different workers. The method will minimize a source of error, especially in repeated tests and in comparative work generally, and may assist in those "border-zone" cases of mild or doubtful infection and in cases which have been well treated. It is in these difficult cases that very accurate standardization is essential, but probably less so in frankly positive and negative sera. Other methods may suggest themselves to other workers, but in the meantime, in the writer's opinion, a fixed standard red cell suspension used in unit volume and, as a corollary, the establishment of a uniform value to the term "minimum hemolytic dose" of complement is, if not essential, at least desirable. The adoption of this or a similar method involves extra labor. It does not simplify the technic, it rather adds to the demands on the worker. If, however, there is a gain in accuracy the extra time involved will be well spent.

NONCONCOMITANCE OF SPINAL FLUID TESTS.—H. C. Solomon, Boston. *Archives of Neurology and Psychiatry*, 1920, vol. iii, p. 49.

There is a nonconcomitancy of the inflammatory elements of the spinal fluid commonly tested for in diagnosis of disease of the central nervous system. Any one may be present or absent when the others are present—with the exception that globulin presages an increased amount of albumin. No spinal fluid can be considered negative in which all these tests have not been used. No one element tested for contains the element or fraction that gives another test, except that the total albumin contains the globulin fraction, in part at least. In neurosyphilitic cases receiving treatment these substances disappear at differing rates which vary in different cases, so that no general law can be laid down as to which element is most easily affected by treatment in any particular case, though in general the pleocytosis disappears first. The presence or absence of these products of inflammatory reaction does not always parallel the clinical change in the treated neurosyphilitic patient.

SYPHILITIC SCARS OF THE SPIRIT.—Joseph Collins, New York. *Journal of the American Medical Association*, 1920, vol. lxxiv, p. 1216.

The chief object in calling attention to this variety of cerebral syphilis is to emphasize the fact that although the infection is thwarted and the patient regains what seems to be his health, he is left with a scar of his mind and his emotions which permanently cripples him to a certain degree. It is easy to measure this degree by psychometric test; but the most telling way of expressing it is to say that it has thrown him from the social, civic, marital, financial level that he had attained, which was a commendable one, to a much lower one at which he can barely support himself and can make no contribution to the welfare, the interest or the support of others. Had he been reduced another peg he might have become a hobo, a wanderer, or a charge on his family or the community. Such experiences as these teach us that syphilis of the nervous system is a curable disease; but the lesson that we learn from it is that the earlier the treatment is instituted the greater is the victim's chance of complete functional recovery.

AT WHAT AGE IS THE PROSTITUTE MOST DANGEROUS?—H. Goodmand. *Bulletin of the Porto Rico Medical Association*. San Juan, 1919, No. 123, p. 66.

A large number of public prostitutes were recently examined clinically and serologically in Porto Rico, where the causes of prostitution and the life of the prostitute are those of the United States and other countries. The age of the women varied from thirteen to fifty-six. Altogether, there were 721 prostitutes, including 139 girls under seventeen years of age; of this group, 42

per cent had three- or four-plus Wassermann reactions; 15 per cent of these young girls had active, infectious syphilitic manifestations, such as chancre, mucous patches, or condylomata lata. The age period from 18 to 22 years comprised 388 prostitutes, or 48 per cent of the total studied. Of these 388, 193, or about 50 per cent, were strongly Wassermann positive and 11 had active genital lesions of syphilis. One hundred forty-seven girls fell into the next age period, 23 to 27 years, of whom 45 per cent were serologically positive, and 11 per cent had dangerous syphilitic manifestations. Only 64 women were in the age group of 28 to 32 years, and 43 per cent of these had three- or four-plus Wassermann reactions, but only 4 per cent were with active lesions. Beyond 32 years, the number of women became much smaller, and the percentage of positive Wassermann reactions became much lower, while none showed any active infectious manifestations of syphilis. The series included 422 whites, 304 mulattos, and 65 negresses. Even with such disparity in numbers, the percentage of Wassermann positive cases was constant, about 47 per cent for each color. In the ratio of active syphilitic lesions, however, there was marked difference. The whites gave 10 per cent; the mulattos, 13 per cent; and the negresses only 3 per cent with infectious syphilitic manifestations. The Wassermann tests were done at the Institute of Tropical Medicine and Hygiene, San Juan, Porto Rico.

SYPHILITIC MENINGOMYELITIS—TREATMENT WITH NEOARSENENZOL.—
P. Nicaud. Bulletin et memoires de la Societe medicale des
hopitaux de Paris, 1919, vol. xxxv, No. 29, p. 875.

Cases of complete or relative cure of syphilitic paraplegia are not very uncommon, but the author feels justified in reporting the following observation on a case of very diffuse, severe, and rapidly progressive meningomyelitis, with very unfavorable prognostic features, in the form of immediately complete flaccid paraplegia and very pronounced sensory disturbances, indicating a persistent paraplegia and a serious disablement. Early arsenic treatment with neoarsenenzol had an undoubted prompt effect, and the symptoms were almost entirely relieved in three months, except certain sequelæ noted in the last examination. The patient's syphilitic infection dated back ten years, and the disturbances were not prevented by two series of galyl in February and May of 1917, a few months before the onset of meningomyelitis.

The patient, a soldier of 34 years of age, was admitted to the Fez Hospital suffering from motor disturbances, having been very rapidly progressive and affecting not only the lower limbs, but also the abdominal and lower thoracic muscles. (Impossibility of lateral movements, flexion, extension of the trunk; slight respiratory disturbances with some precordial distress.) The tendon reflexes were greatly dimin-

ished and finally disappeared; the patient presented a bilateral Babinski. The cutaneous, cremasteric, superior and inferior abdominal reflexes were completely lost. The sensory disturbances continued to extend upwards and total anesthesia to touch, pain, and temperature, developed after a state of hypoaesthesia of the lower limbs, the abdomen and the thorax.

The very rapidly progressive disturbances stopped at once after the beginning of treatment and subsided very promptly under its influence. The disturbances of the sphincters in the form of incomplete urinary and fecal retention, improved very rapidly as a result of the medication. The patient received a first series of eight neosalvarsan injections (10, 20, 30, 45, 60, 75, 90, 90 centigrams). After the first injection (0 gr. 10), the actively progressive symptoms became assisted and after the second injection (0. gr. 20), there was a very rapid subsidence of the sensory disturbances, which had almost entirely disappeared at the time of the eighth injection. The motor disturbances subsided likewise, although more slowly. The flaccidity diminished. The abdominal and thoracic motor disturbances improved very rapidly, and the tendon reflexes reappeared in the lower limbs. Very rapid progressive reestablishment of the voluntary movements of the lower limbs followed. After a pause of twelve days, the treatment was resumed and the patient again received neosalvarsan injections (15, 30, 45, 60, 75, 90, 90, 120 ctg.). About the twelfth injection, walking on crutches became possible and continued to improve at a rapid rate. The sensory disturbances had entirely disappeared and all the cutaneous reflexes had returned to normal. In view of the very positive persistence of the Wassermann reaction in the blood, a new series of neosalvarsan injections was started at the end of about two weeks.

DELAYED ARSENICAL POISONING.—George S. Strathy, Captain C. H. V. Smith, and Beverly Hannah, Toronto, Canada. *Lancet*, 1920, vol. cxcviii, p. 802.

Fifty-eight cases of delayed poisoning following administration of salvarsan and mercury were observed. Forty-seven of these showed symptoms referable to the liver—namely, jaundice, decreased digestive power, and liver atrophy. Eight of these were fatal and at autopsy showed marked atrophy of the liver. Atrophy of the liver may be marked in cases which ultimately recover. This condition can be diagnosed by x-rays. Dermatitis occurred in eight cases. Five were severe with marked exfoliation. Peripheral neuritis was observed in two cases. Albuminuria was present in over 50 per cent of the cases. Edema was found in two cases. The onset of the symptoms seldom occurred until five weeks after the administration of salvarsan had ceased. The earliest symptoms of salvarsan poisoning of the liver were—bile in the urine, albuminuria, loss of appetite and jaundice.

These symptoms should be looked for in all patients receiving salvarsan treatment, and on their appearance the administration of salvarsan should cease. By x-ray examination atrophy of the liver may be diagnosed at an early stage. Where evidence of liver damage is present the diet should be reduced to a minimum. Dermatitis with atrophy of the liver occurred in one patient who received arsenic in the form of Fowler's solution, 5 minims. The author believes these were cases of delayed arsenical poisoning.

SOME THEORIES OF SYPHILIS.—Joseph Wittenberg, Brooklyn. *New York Medical Journal*, 1919, vol. cx, p. 669.

If the suggestion the author has made as to the difference in action of mercury and arsphenamine on antibody-forming tissues is correct, it may be said that the use of both these drugs simultaneously is advisable to secure the maximum amount of antibody as soon as possible. It is quite likely that both drugs together may act more energetically than either, until the germs become "fast" and the tissues overstimulated, but, since it is impossible with any means at our disposal at present to bring about the destruction of all the spirochetes in the body in one of the short periods that these drugs act favorably, it seems that it is best to use them separately. Arsphenamine, a powerful spirocheticide and an effective builder of immunity, if used in moderation, may be employed first; and when this preparation must be stopped, the weaker spirocheticide and less dangerous immunity builder, mercury, is administered while the "fastness" of the germs and immunity building cells to the arsenic is disappearing. A period of rest, long enough to permit the first drug used to be eliminated completely and the spirochetes and immunity-building tissues to resume their sensitiveness to that drug, should follow and the course be repeated. It is known that the current of the cerebrospinal fluid is from above downward. It is also known that while most of the fluid escapes through the venous circulation, a small amount escapes along the nerve roots under the sheaths formed about them by the extension of the cerebrospinal meninges. It is along this path, according to the author's theory, that the arsenical compounds, which have penetrated into the cerebrospinal fluid after intravenous injection of the arsphenamine, reach the ganglia on the posterior nerve roots which are often involved in tabes.

SEVERE DERMATITIS DURING TREATMENT WITH NOVARSENOBILLON.—L. G. Leonard, Manchester, England. *British Medical Journal*, 1919, No. 3076, p. 773.

The points of interest in this case appear to be: (1) The occurrence of so severe a dermatitis and toxemia after the administration of only 1.9 grams of novarsenobillon. (2) The high tem-

perature recorded—105° F. (3) The simultaneous occurrence of three distinct types of eruption—maculopapular, scarlatiniform, and urticarial. (4) The marked general adenitis at the onset, present before the lesions, other than the scalp, had become pustular. The negative Wassermann reaction of October 8th; that on July 24th, before treatment commenced, being strongly positive.

A COMPARISON OF TWO METHODS OF ADMINISTERING ARSENOBENZOL COMPOUNDS IN SYPHILIS.—H. E. Gibson, London. *British Medical Journal*, 1920, No. 3082, p. 114.

Advantage seems to lie with the prolonged course, partly owing to the lesser incidence and violence of reactions, and partly because the total results are better than with the concentrated course; this especially applies to secondary cases. Should a patient showing only a primary sore have urgent reasons for wanting a short course, the concentrated course may be given, but otherwise it is better to spread the treatment out over a longer period.

SUGGESTIONS TO CONTRIBUTORS

"The four rules for the preparation of an article will then be: (1) Have something to say; (2) Say it; (3) Stop as soon as you have said it; (4) Give the paper a proper title."¹

Let your phraseology express one meaning and one only. Be clear.²

Manuscript.—Manuscripts should be typewritten, with wide margins, and double spaced, on one side of paper 8½ by 11 inches in size. The original copy should be sent to the "Journal" and the carbon copy retained by the author. Number the leaves consecutively, beginning with the title page. Put your name and address on the manuscript.

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Arrangement.—As authors are quoted in the text give each a number in the order of citation, and number the bibliographic reference with the same number. Arrange the references in a list at the end of the article in the order of the numbers (see below), or arrange items in alphabetical order according to last names of authors, and distinguish between articles by the same author by the use of the date after his name in the text.

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